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RAND EUROPE

Mental Health Retrosight

Perspectives

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Prepared for the Alliance of Mental Health Research Funders

The project described in this report was supported in Canada by the Graham Boeckh Foundation, Alberta Innovates Health Solutions, and the Canadian Institutes of Health Research; in the UK by the National Institute for Health Research; and in the USA by the National Institute of Mental Health.

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Preface

Mental Health Retrosight was a three-year international project that aimed to investigate the translation and payback from mental health and neuroscience research, with a particular focus on schizophrenia. It looked at the development of research over a 20-year period in Canada, the USA and the UK.

The project was supported in Canada by the Graham Boeckh Foundation, Alberta Innovates – Health Solutions, and the Canadian Institutes of Health Research; in the UK by the National Institute for Health Research; and in the USA by the National Institute of Mental Health. It was the first project funded through the Alliance of Mental Health Research Funders, a joint initiative between the Graham Boeckh Foundation and RAND Europe. The network was established as a 'think tank without borders' that would undertake research and analysis into mental health research funding.

This report presents the full set of backward-tracing perspectives. This is intended to complement the other reports associated with this study, which describe the findings and policy provocations, the methods and methodology, and the forward-tracing case studies.

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CHAPTER 1 Introduction

This report presents the story of the development of six interventions aimed at improving mental health care. These narratives were assembled as part of Mental Health Retrosight, an international project which examined the attributes of research that lead to successful translation into patient benefit.

We identified the six interventions through a combination of a survey, a comparison of clinical guidelines over time and across the three countries of the study (Canada, the UK and the US) and the input of our subject expert advisors.

Having selected the interventions, we then tried to develop narratives for each through a combination of telephone and face-to-face interviews, reviews of archived material and literature reviews. As we developed these, it became clear that the scope of the subjects covered and the contested nature of the fields meant it was not feasible to construct a single, definitive narrative for each intervention. Instead we concentrated on consulting a variety of sources and establishing a balanced perspective. This is why we choose to refer to these narratives as 'perspectives' rather than histories or case studies, as they represent one perspective on the developments, albeit one drawn from a reasonably wide variety of diverse sources.

The six interventions we examined were:

- The use of **cognitive behavioural therapy,** a form of psychosocial or 'talking' therapy, as a treatment for schizophrenia.
- The recognition of the value of **early intervention** in schizophrenia and the realisation that treatment was often delayed.
- The use of **supported employment** as a way to help people with schizophrenia gain and maintain employment.
- The development, introduction, removal and re-introduction of **clozapine,** the first of the second generation anti-psychotic drugs.
- The recognition of, and moves to address, the **metabolic side effects of second generation antipsychotics.**
- The recognition of the role of cognitive deficits in schizophrenia, and efforts to develop **cognitive-enhancing drugs** to address them.

The analysis was iterative and took a narrative approach. A researcher who had not been involved in assembling the perspectives read and reviewed the full set, extracting and

describing the attributes that appeared to have either promoted or hindered translation. Further details of the selection and construction of the narratives are provided in the *Methods and Methodology Report.*[1]

We are publishing the perspectives to increase the transparency of our research process. We hope the publication will allow other researchers to build on our work, through adding further cases or refining existing ones. During the project we refined and developed the methods and structuring of the cases, learning from some cases in conducting others. However, it should be noted that the structure we were striving towards was one that facilitated analysis, and not one that necessarily provided the most succinct and compelling narrative.

In addition, because of the diverse nature of the cases and their stages of development, and in some cases commercial sensitivities, there are differences in the information we were able to source for each. Although we tried to develop a standard structure for all of the perspectives in order to facilitate comparison, we are still some way from satisfactorily achieving this and variations exist across the set of perspectives.

We hope that the perspectives presented in this report will provide food for thought for those interested in the genesis of advances in mental health care, and that they will support future research in the area.

[1] Guthrie, S., Wooding, S., Pollitt, A., Pincus, H. and Grant, J. (2013). *Mental Health Retrosight. Methods and methodology report.* Cambridge, UK: RAND Europe.

CHAPTER 2 Supported employment

2.1 Summary

Supported employment is a form of vocational rehabilitation, used in schizophrenia care and more widely in mental health care. It emphasises placing clients in socially integrated work settings, followed by training and ongoing support with no time limits, rather than training clients prior to placement.

Vocational rehabilitation in mental health has its origins in early mental hospitals and the work activities patients often undertook in maintaining them, but it was not until the beginnings of the clubhouse movement, which became particularly popular in the US in the 1950s, that rehabilitation became the primary focus of such work (Dew and Alan, 2005; Pratt, et al. 2007). In these programmes, which were non-clinical and focused on work, housing, socialisation and recreation needs, clubhouse members were encouraged to work alongside staff on tasks necessary to maintain the clubhouse.

The broader concept of psychiatric rehabilitation became increasingly prominent in the mental health field during the 1960s, as programmes of hospital closures began and the need for appropriate community care became clear. As patients were discharged to community settings, their disabilities became more obvious and a vast range of rehabilitation programmes were developed.

The vocational rehabilitation services developed during this period utilised a 'train-place' approach. This emphasis on the need for substantial training and preparation before entering employment forms the basis for models such as sheltered workshops, hospital-based work programmes and job clubs. These programmes tended to be delivered quite separately from community mental health services (Newman, 1970). Attempts to bridge this gap in services in the US during the 1960s tended to centre on mental hospitals and focused on rehabilitation for people with chronic conditions, but the growing movement towards community mental health care emphasised the need for such services to be provided through community mental health facilities.

During the 1980s and early 1990s traditional 'train then place' programmes began to fall out of favour in the US (although many well-established programmes continued to operate) due to a lack of convincing evidence of effectiveness and a major shift in attitudes in the field of psychiatric rehabilitation. This changing landscape was characterised by the emergence of the 'recovery' movement, the increasing acceptance of psychosocial rehabilitation, and an increased emphasis on consumer choice, factors which were also reflected in changes to US legislation at the time.

As in the US and UK, Canada had a long history of vocational rehabilitation programmes, with programmes in sheltered work environments having existed throughout much of the twentieth century. In the 1970s some consumer-run businesses began to appear (Menear: Personal Communication, 2012), particularly as part of an Ontario movement that emerged quite independently of US trends, and this period saw growing diversity in the range of vocational services available (Latimer: Personal Communication, 2011). During this time services emerged in response to service user needs that became apparent with the closure of mental hospitals and move towards community care; there was no concerted effort from authorities at the time to implement any particular model (Menear: Communication, 2012).

In 1993 the Individual Placement and Support model of supported employment was put forward at New Hampshire-Dartmouth Psychiatric Research Center in the US (Becker and Drake, 1993), following studies that were first initiated in 1990 (Drake, et al. 1994). This simple, clearly-defined programme became the subject of numerous randomised controlled trials and demonstration projects, and as evidence for its effectiveness mounted, it became recognised as an evidence-based practice and was rolled out systematically across an increasing number of US states. Practitioners in both Canada and the UK became aware of the growing literature on IPS and the first programmes in these countries were launched around 2000.

Although there have been a number of barriers to the widespread adoption of IPS, not least some evidence that its effectiveness may depend on factors such as the strength of the local economy and nature of welfare systems, as well as some resistance to change by practitioners, its use is recommended by national clinical practice guidelines in both the US and UK (the nature of the Canadian health and social care system is such that vocational rehabilitation is a provincial responsibility).

2.2 Case study scope

Supported employment is a form of vocational rehabilitation which emphasises rapid job search for competitive jobs in socially integrated work settings followed by ongoing support with no time limits (eg Cook, et al. 2005). The emphasis is on rapid job search, in contrast to traditional vocational rehabilitation approaches, which tend to offer a sheltered work environment in combination with an extensive preparatory phase of prevocational training. The most researched model of supported employment is the Individual Placement and Support model (Becker and Drake, 1993), emerging in the early 1990s in the US.

In completing this case study, interviews were conducted with experts involved in both research and implementation in the US, the UK and Canada. In the latter, as the provision of mental health services is a provincial responsibility, services have developed differently from province to province. For the purposes of this case study, interviews were conducted with experts who had particular knowledge of Ontario, Quebec and British Columbia, the three most populous provinces (accounting for 75% of the population). Interviews were complemented with an extensive document and literature review. Interviewees were: Gary Bond (Dartmouth Psychiatric Research Centre, US), Tom Burns (Oxford University,

UK), Eric Latimer (McGill University, Canada), Kim Calsaferri (Vancouver Coastal Health, Canada) and Matthew Menear (Université de Montréal, Canada).

2.3 Timeline of key events

Key:

Canada
United Kingdom
United States
Other

Date	Event
Late 1940s	Clubhouse movement founded on the premise that work is important and that clubhouses can provide a stepping stone to competitive employment
1960s onwards	Widespread programmes of mental hospital closures highlight the need for better community care
1970	Instant Placement model (Newman, 1970)
1970s	Vocational rehabilitation services begin to become readily accessible to people with psychiatric disabilities, through the 1973 Rehabilitation Act (establishing the RSA), through NIMH establishing the Community Support Program, and for veterans through the VA's Compensated Work Therapy Program (Pratt, et al. 2007)
1974	PACT model (initially the 'training in community living program') (Stein and Test, 1980; Stein, et al. 1975)
1978	NIMH and RSA establish two vocational rehab research and training centres
1980	NIMH, RSA, the National Institute on Handicapped Research and Council of State Administrators of Vocational Rehabilitation enter into a cooperative agreement
1981	Conference improving interagency collaboration between vocational rehabilitation and mental health agencies
1980s	Workshop approaches to employment shown to be unsuccessful
1980s	Evidence growing of ability of people with severe developmental disabilities to live and work successfully in community
1980s onwards	Consumer movement gathers pace

1980s onwards	Growing emphasis in the medical field on helping patients make informed choices by providing information about options (Wennberg, 1988; Cook, 1992)
1980s onwards	Recovery movement emphasises individual's role in defining improvements in their lives
1980s onwards	Psychosocial Rehabilitation perspective gained prominence (originating in US but reaching more widely), emphasised individual strengths and potential, and stressed power of work as a re-integrative force (see Menear et al. 2011)
1984	Madeline Will (US Office of Special Education and Rehabilitative Services) proposed model for transition of youths with disabilities from school to work
1984	Interagency workgroup set up to improve services to the 'chronically mentally ill'
1984	Developmental Disabilities Assistance and Bill of Rights Act. Growing dissatisfaction and unemployment
1984	US Department of Health and Human Services reports that 90,000 developmentally disabled students leave school each year without adequate services or jobs
1985	Supported employment developed for developmental disabilities (Wehman and Kregel, 1985)
1986	Wehman model for physical disability
1986	Amendments to Rehabilitation Act introduced supported employment as an 'eligible service option for persons with severe handicaps'
1987	Supported employment adapted for psychiatric rehabilitation: the Choose-Get-Keep model (Danley and Anthony, 1987)
1987	Special issue of Psychiatric Rehabilitation Journal introduced the concept of supported employment
1988	Graham Report in Ontario draws on ideas of consumer/survivor movement to call for vocational support, including supported employment
1993	Individual Placement and Support model (Becker and Drake, 1993)
1994	Start of RCTs of IPS
1995	Employment Intervention Demonstration Program funded by SAMHSA
1995	36,000 people with mental illness now employed in supported employment positions in the US
Mid-1990s	Some Canadian vocational rehabilitation agencies move towards

onwards	implementing supported employment, often gradually
1997	Fidelity scale developed to measure adherence to programme standards and provide operational definitions for key ingredients (Bond et al. 1997): aimed to prevent model diffusion
1997	New government re-emphasises 'Welfare to Work' and aims to foster employment opportunities for disabled people
1998	Robert Wood Johnson Conference identifies supported employment as one of six evidence-based practices in mental health
1998	Implementing Evidence-Based Practices Project begins (see Mueser, et al. 2003)
Early 2000s	First IPS programmes emerge in Canada
2001	Cochrane review concludes supported employment superior to pre-vocational rehabilitation (Crowther, et al. 2001)
2001	Johnson & Johnson – Dartmouth Community Mental Health Program begins with three site pilot
2003	President's New Freedom Commission on Mental Health Report published in the US
2004	VA Comprehensive Mental Health Strategic Plan: expansion of SE within the VA
2004	Social Exclusion Unit endorses IPS in the UK
2005	Disability Discrimination Act: definition of mental health changed to cover more people
2005 -	EIDP publishes first findings
2006	First Canadian RCT of IPS published
2006	Department of Health endorses IPS in commissioning guidelines
2006	Government's Social Exclusion Task Force endorses IPS in action plan
2006	Department for Work and Pensions Green Paper 'A new deal for welfare: empowering people to work'
2007	First European RCT, EQOLISE, shows applicability in Europe, but also relationship between success and economic disincentives
2007	PSA Target 16 to increase the proportion of adults in contact with secondary mental health services in employment, education or training
2007	Results of SESAMI study published, making recommendations for UK
2008	Only 2% of target population in US have access to evidence-based employment services (SAMHSA, 2009)
2009	Government publishes a series of documents stating that IPS should be

	used in mental health services
2010	SWAN RCT casts doubt on effectiveness of IPS in the UK, but flaws in its methodology are highlighted

2.4 Narrative

Historical context of vocational rehabilitation

Vocational rehabilitation in mental health has its origins in early mental hospitals and the work activities patients often undertook in maintaining them, but it was not until the beginnings of the clubhouse movement, which became particularly popular in the US in the 1950s, that rehabilitation became the primary focus of such work (Dew and Alan 2005; Pratt, et al. 2007). In these programmes, clubhouse members were encouraged to work alongside staff on tasks necessary to maintain the clubhouse. The aim of this was to build members' confidence, self-esteem and basic work skills, and while the primary aim of these 'work units' was to provide members with these benefits, some also considered that they might provide suitable 'prevocational' skill development for people to enter regular employment (eg Marrone, 1993).

The broader concept of psychiatric rehabilitation became increasingly prominent in the mental health field during the 1960s, as programmes of hospital closures began and the need for appropriate community care became clear. As patients were discharged to community settings, their disabilities became more obvious and a vast range of rehabilitation programmes were developed.

> Rehabilitation developed as a sub-specialty and was really fairly over-engineered. It became very preoccupied with breaking down disabilities into smaller and smaller facets and having stepwise [i.e. gradual work exposure] treatment programmes to address disabilities and deficits. And that worked very well in some aspects of rehabilitation[…] The problem with it is that it never translated as successfully into gaining work
>
> (Burns: Personal Communication, 2011)

The vocational rehabilitation services developed during this period utilised a 'train-place' approach. This emphasis on the need for substantial training and preparation before entering employment forms the basis for models such as sheltered workshops, hospital-based work programmes and job clubs. These programmes tended to be delivered quite separately from community mental health services (Newman, 1970). Attempts to bridge this gap in services in the US during the 1960s tended to centre on mental hospitals and focused on rehabilitation for people with chronic conditions, but the growing movement towards community mental health care emphasised the need for such services to be provided through community mental health facilities.

1970: Instant Placement model (Newman)

The traditional vocational rehabilitation approaches of clubhouses and sheltered workshops appear to have remained unchallenged until 1970, when Leonard Newman suggested that in contrast to the train-place model, it was better for those with serious mental illness to be placed immediately in jobs and then receive ongoing training (Newman, 1970). His basis for this was that using the criteria developed to judge suitability for work of physically disabled people, which emphasised previous social and vocational functioning, resulted in those with mental disorders being excluded from programmes. Even when people with mental disorders were accepted on to programmes, Newman suggested that prevocational training may not be beneficial, but may act to reinforce feelings of dependency and increase anxiety. He argued that this extensive generic training prior to placement was only appropriate for disabilities with clearly defined limitations (eg loss of a particular sensory or motor function) and a stable time course for recovery.

Although Newman's ideas were not formally picked up at the time of his paper, the practice of minimising prevocational training may have existed informally. Burns commented that when he first worked in psychiatry, at a rural hospital in Scotland, there had been a member of staff who found local employment for many patients. Bond, similarly, commented that a study he had carried out in 1979 involved the successful removal of the training phase from a transitional employment programme at Thresholds, a rehabilitation services provider in Chicago (Bond and Dincin, 1986). This study was based on the suggestion that the work crews at Thresholds were delaying entry into paid employment and so limiting improvements in vocational outcomes (Dincin and Witheridge, 1982). When conducting a literature review for this study, Newman's 1970 paper was one of very few Bond found that discussed the idea that prevocational training was not important (Bond: Personal Communication, 2011).

1970s: Recognition of importance of vocational rehabilitation for people with psychiatric disability

Throughout the 1970s there was growing recognition in the United States of the importance of vocational rehabilitation for people with psychiatric conditions. A number of changes to legislation and welfare systems occurred over this period.

In 1973 the US Congress passed the Rehabilitation Act, a piece of legislation previously vetoed twice by President Nixon on the grounds that funding levels were too high and that a new focus on 'independent living' for disabled people and the wider welfare considerations this entailed may detract from the Act's primary focus on employment (Nixon, 1973). One component of the Act was the establishment of the Rehabilitation Services Administration (RSA), an agency tasked with, among other things, providing vocational rehabilitation services to the most severely disabled and those under-served in the past, as well as developing innovative new methods in vocational rehabilitation. This helped improve the accessibility of services and also allowed for the provision of state level funding to support programmes (Pratt, et al. 2007).

In 1978 the RSA entered into a collaborative agreement with the National Institute of Mental Health (NIMH) to establish two rehabilitation research and training centres

focused on psychiatric disabilities (Anthony and Blanch, 1987). This had come about in part as a result of the impact of NIMH's Community Support Program (CSP), an initiative looking at how best to provide community-based rehabilitation services to the mentally ill. Bond commented that this programme was a valuable funding source in establishing the evidence base for supported employment, as it was very 'risk-taking' and was willing to fund innovative demonstration projects. Following the establishment of the Substance Abuse and Mental Health Services Administration (SAMHSA), the CSP fell under the new agency's remit. According to Bond, this reorganisation led to a de-emphasis on rigorous new research, as SAMHSA had an express mission not to devote funding to research.

1980: The advent of evidence-based medicine in mental health services

It has been suggested that an important factor in the development of supported employment programmes was the rise of evidence-based medicine in mental health and its interaction with the evolving models of community-based psychosocial interventions (Burns: Personal Communication, 2011). While randomised controlled trials had been the norm for some time for pharmacological interventions, psychosocial or health services interventions were rarely subject to the same level of scientific scrutiny. According to Burns, a major factor in changing this situation was the publication of a number of trials demonstrating the effectiveness of Assertive Community Treatment by Leonard I. Stein, Mary Ann Test and colleagues in Madison, Wisconsin (eg Stein and Test, 1980).

> You've got a high quality RCT with a very powerful result, but which described the intervention; indeed prescribed the intervention[…] And I think if you look at the take-off of community based psychiatric research studies, it goes exponential the next three to four years after that study […] people began to expect service structures to be exposed to the same sort of scientific regulation that they'd been used to for a decade by then with drugs.
>
> (Burns: Personal Communication, 2011)

1980s: Increased cooperation between agencies

Following the increased focus on vocational rehabilitation that had emerged during the 1970s, the 1980s began with NIMH, the Rehabilitation Services Administration, the National Institute on Handicapped Research and Council of State Administrators of Vocational Rehabilitation in the US entering into a cooperative agreement that led to a 1981 conference on interagency working. One of the outcomes of this conference was the decision that research was needed on how collaboration between agencies affected vocational outcomes for service users, and the first studies looking at cooperation between the mental health system and vocational rehabilitation services were published a few years later (Dellario, 1985; Rogers, et al. 1989). These studies concluded that with existing levels of funding, improved vocational outcomes could be achieved solely through closer working between mental health and rehabilitation agencies. The 1981 conference also led to the formation, in 1984, of an interagency work group to look at improving services for people with a psychiatric disability.

At around the same time in the field of developmental disabilities, Madeline Will was an influential figure in the federal government, where she was Assistant Secretary of the Office of Special Education and Rehabilitation Services (OSERS) (Bond: Personal Communication, 2011; Anthony and Blanch, 1987). In response to a report by the Office of the Inspector General of the Department of Health and Human Services, which claimed that each year 90,000 developmentally disabled students were leaving school without adequate services or jobs, Will proposed a model for the transition of youths with disabilities from school to work and adult life (Will, 1984).

Both the interagency working group with its specific focus on mental health and Madeline Will in OSERS were instrumental in advocating for supported employment programmes in vocational rehabilitation and were key in securing its inclusion in the amendments to the 1986 Rehabilitation Act (Bond: Personal Communication, 2011; Pratt, et al. 2007).

1986: Amendments to Rehabilitation Act

Driven by the findings of the interagency work group, these amendments defined supported employment as a promising new practice and set out a system for funding its implementation. Three critical elements of supported employment were identified: (i) competitive employment; (ii) an integrated work setting; and (iii) ongoing support services (Rusch and Hughes, 1989). Bond commented: 'The Rehab Act legitimised the concept of supported employment, so in that sense it was crucial… but [it] by no means mandated what kind of services be provided, except in very broad strokes.' (Bond: Personal Communication 2011).

1986: Wehman model of supported employment for people with developmental disabilities

As discussed above, throughout the 1980s support had grown for the idea that vocational rehabilitation was both a valuable and achievable aim for people with disabilities, and legislative changes had made it possible for this support to be received. However, there had been little focus on how best to deliver vocational services, either in mental health specifically, or more generally in the disability field. Traditional clubhouse or sheltered workshop approaches prevailed, although evidence was beginning to build of their ineffectiveness in terms of employment outcomes (eg Bellamy, et al. 1986; Bond, 1992; Bond, 1998).

Wehman (1986) argued that traditional sheltered workshops isolate people from mainstream society. Instead, and in line with Newman's suggestion some fifteen years previously that had received little attention, he proposed that sheltered prevocational training be minimised, with clients entering competitive roles as soon as possible. Ongoing support and training was then provided by way of a 'job coach', who might work alongside the client, either for the entire time, or being gradually phased out. This 'place-train' approach was in stark contrast to the 'train-place' approach used traditionally in vocational rehabilitation services. Unlike later models of supported employment that would emerge in the mental health field, the notion of client choice was not a prominent feature of the approach (Bond: Personal Communication, 2011).

1987: Choose-Get-Keep model (Danley and Anthony, 1987): tailoring supported employment for people with mental illness

As described above, the model of supported employment proposed by Wehman was developed as a fairly general approach for people with severe disabilities. However, some in the psychiatric rehabilitation field believed that it may have needed to be tailored more specifically to meet the needs of people with schizophrenia and other severe mental illnesses. This tailoring was first undertaken by Bill Anthony, Karen Danley and colleagues at Boston University, who proposed the Choose-Get-Keep model (Danley and Anthony, 1987) as an alternative to the traditional approaches to vocational rehabilitation. Although changes in the 1970s had improved the accessibility of these traditional vocational services for people with mental disorders, the employment outcomes from them were poor. Anthony and colleagues conducted several reviews of outcomes during the 1970s and 1980s (eg Anthony, et al. 1978; Anthony and Dion, 1986), finding a full-time, competitive employment rate of 20–25% for all people discharged from mental hospitals and a much lower rate for the most severely affected (eg Farkas, et al. 1987; Spaniol, et al. 1984).

In response to this, Anthony and Blanch (1987) proposed bringing 'supported employment', in the form of the Choose-Get-Keep model, to the psychiatric rehabilitation field. This approach differed from traditional vocational rehabilitation in emphasising that everyone can work in a 'normal' work setting with the appropriate support, and that work cannot be isolated from the context of the individual's life, suggesting that holistic support was needed. A key element of the model is the notion of client choice, something which was gaining increasing prominence throughout the mental health field and healthcare more widely, particularly in relation to patients being able to make an informed choice about their treatment (eg Wennberg, 1988). Whereas previous programmes had attempted to 'match' clients to jobs, the Choose-Get-Keep model emphasised the importance of the client being involved in this process and choosing the kind of work that they would do. The model suggests that this is done through an intensive phase of prevocational preparation where the client gains a better understanding of their own skills and employment aspirations.

The article setting out the key principles of the Choose-Get-Keep model (Anthony and Blanch, 1987) was published in a special issue of the *Psychosocial Rehabilitation Journal*, which pulled together the state of knowledge in the field at the time. Bond noted that for him this special issue seemed to be the origin of supported employment becoming more widespread in the mental health field (Bond: Personal Communication, 2011), something which appears to be supported by the number of citations received by Anthony and Blanch's article on the Choose-Get-Keep model.[2]

[2] At that time the journal *Psychiatric Rehabilitation* was not indexed in Web of Science and so it is not possible to identify a precise number of citations. The article appears to be highly cited according to Google Scholar (and is the most highly cited in that issue of the journal), but due to uncertainty around the compilation method of these citation figures we do not include them in the case study.

1988: The Graham Report is published in Ontario

Up until the 1980s, vocational rehabilitation in Canada resembled the situation in the US, with a variety of programmes based in sheltered work environments dominating provision (Menear: Personal Communication, 2012). There was also a similar move to close beds in specialist psychiatric hospitals throughout the 1970s and 1980s, although the timing and pace of this trend varied somewhat from province to province (Sealy and Whitehead, 2004).

While the focus of mental health services was moving increasingly towards community-based initiatives, in Ontario there was an acknowledgement that the existing services were not sufficient and needed to be further developed (Menear: Personal Communication, 2012). Between 1985 (when a Liberal government replaced the Progressive Conservative Party) and the publication of the Graham report in 1988, funding for community mental health programmes increased by 65%, while the Premier announced in 1987 that funding in this area was to double by 1990 (Ontario Ministry of Health, 1988).

The Graham report set out a plan for a community-focused, integrated mental health care system for Ontario, while highlighting the fact that in many regions of the province, vocational rehabilitation services were not widely available. This report drew heavily on the consumer movement that was rapidly gaining momentum at the time, and emphasises joint working with service users and families to enhance individuals' competencies. Menear commented that this shift in perspective is also reflected in some of the language used in the document, which begins to reflect more of a recovery focus (Menear: Personal Communication, 2013). However, while the report set out clear principles for the organisation of services, it included little detail on what form these services should take.

1993: Individual Placement and Support model (Becker and Drake, 1993)

Drawing on a number of other theories, models and findings in the field of vocational rehabilitation, it was Robert Drake, Deborah Becker and their colleagues at the New Hampshire-Dartmouth Psychiatric Research Center who crystallised much of the thinking in a still fragmented field in the early 1990s. This fragmentation may have actually been a positive thing in the early years of supported employment: some feared that premature standardisation might eliminate the innovative thinking which had led to its initial development (Pratt, et al. 2007).

However, in 1993, Becker and Drake proposed the Individual Placement and Support (IPS) model as a means of unifying existing supported employment approaches (Becker and Drake, 1993), and aimed to build up an evidence base around its eight key principles (see Box 1).

> We do not view this approach as a distinct supported employment model. Instead, it is intended as a standardization of supported employment principles in programs for people with severe mental illness, so that supported employment can be clearly described, scientifically studied, and implemented in communities.
>
> (Bond, et al. 2001)

Building on the Choose-Get-Keep model, IPS also emphasises the importance of client choice in the job search. However, unlike its predecessor, there is a strong focus on completing this process rapidly, a principle more akin to the place-train approach advocated by Wehman's (1986) model for developmental disability. Becker and Drake (2003) argue that 'the idea of preemployment training assumes that learned skills will transfer to different situations and different tasks and, for individuals with major mental illness, this often turns out to be inaccurate'. They go on to add that the training environment is often unrealistic and unchallenging – very different to competitive jobs that clients themselves have chosen. Instead, time-unlimited support is provided during employment.

Key principles of the IPS model:

1. A focus on competitive employment
2. Eligibility based on consumer choice
3. Rapid job search
4. Integration of mental health and employment services
5. Attention to consumer preference in the job search
6. Individualised job supports
7. Personalised benefits counselling
8. Systematic job development

Box 1: The seven key principles of IPS (Drake, et al. 2012)

These developments may also have reflected wider trends in the mental health care field at the time, as noted by Cook and Pickett (1994) in their discussion of trends in vocational rehabilitation:

> How the vocational rehabilitation field responds to this newly politicized, increasingly assertive, and more 'service-savvy' group of consumers remains to be seen. The use of older models in which clients engage in long periods of prevocational preparation or where they are offered sheltered or temporary work before integrated, permanent jobs may be questioned by these clients.
>
> (Cook and Pickett 1994)

An element included previously by neither Wehman nor the Choose-Get-Keep model was the emphasis on the close integration of mental health services and rehabilitation services. The inspiration for this came from the growing evidence of the effectiveness of Assertive Community Treatment (Stein and Test, 1980), as discussed above, which pioneered a community-based approach combining mental health and social services. These multidisciplinary teams had successfully incorporated a form of supported employment alongside other services, avoiding fragmentation of services and diffusion of responsibility in the system (Becker and Drake, 2003).

> We realised that we don't want to work within the freestanding comprehensive rehabilitation agencies, but rather that employment services should be offered in mental health centres. That was a huge breakthrough in the thinking. I think that was Bob Drake and Debbie Becker who really saw that so clearly and that was so crucial in the evolution.
>
> (Bond: Personal Communication, 2011)

Subsequent research looking at the benefits of integrated vs non-integrated services has suggested that the key advantages are: (i) more effective engagement and retention; (ii) better communication; (iii) opportunities for clinicians to understand and focus on

employment; and (iv) incorporation of clinical information into vocational plans and services (Drake, et al. 2003).

1994: First day treatment conversion study published

Closure of mental hospitals had increased the need for an alternative form of service delivery, a situation which had led to the introduction of 'partial hospitalisation' or 'day treatment' (as mandated in the US Community Mental Health Center Act of 1963). Drake et al. (1994) published an account of a community mental health centre that abolished its day treatment programmes because of budget cuts, replacing it instead with a supported employment programme. When compared to another site that retained its day treatment programme along with traditional vocational services, people participating in the supported employment programme had a greater likelihood of obtaining competitive employment, without any increase in adverse outcomes. A number of subsequent studies also found similar results (eg Bailey, et al. 1998; Torrey, et al. 1995), which, according to Bond, were very influential in demonstrating the advantages of supported employment programmes over traditional services (Bond: Personal Communication, 2011).

1994: Randomised Controlled Trials begin

Following the efforts to standardise supported employment with the IPS model, its developers and other researchers in the field began to conduct empirical research to test its effectiveness against existing alternative models of vocational rehabilitation and test key the principles that the IPS model sets out. The first randomised controlled trials of vocational rehabilitation services were carried out to test the programme's effectiveness in improving employment outcomes (eg Drake, et al. 1999; Drake, et al. 1996; Lehman, et al. 2002). Generally these studies found that IPS was superior to other interventions when comparing rates of obtaining competitive employment (Bond, et al. 2008), although some did question the superiority of IPS in increasing job retention (eg Lehman, et al. 2002).

Many of these studies were supported by NIMH and SAMHSA, both of which were engaged in the expansion of evidence-based practices in mental health. Other funding was available from US state-level rehabilitation agencies, while smaller grants (albeit unlikely to be sufficient for RCTs) could be obtained from the National Institute of Disability and Rehabilitation Research (Bond: Personal Communication, 2011).

1995: Employment Intervention Demonstration Program (EIDP) begins

One of the earliest studies to compare vocational interventions in a systematic way was the Employment Intervention Demonstration Programme (EIDP; Cook, et al. 2002). This multisite collaborative study took place in eight US states and involved eight demonstration sites, a coordinating centre at the University of Illinois, and the Center for Mental Health Services (CMHS) of SAMHSA. The study compared several different employment programmes, including Individual Placement and Support, Program of Assertive Community Treatment, and the International Center for Clubhouse Development programme. Although various studies had shown positive results for some of these programmes, little was known at this time about the relative effectiveness of them.

The evaluation was designed to incorporate a multisite study within a series of site-specific, stand-alone studies in order to maximise learning from individual sites, while maintaining the ability to conduct a robust comparison. Other approaches considered, and subsequently dismissed, were to run a series of independent studies at the sites (something which the CMHS had done previously) or to use individual sites simply for data collection, with all analysis done at the aggregate level. Sites applied to participate and were assessed on the rigour of their evaluation design, including aspects such as random assignment to conditions, using fidelity assessments of service interventions, maintaining high inter-rater reliability and the quality of statistical analysis plans. It was also important for applications to detail a comprehensive dissemination plan to reach a range of stakeholders through different forms of communication.

The coordinating centre and initial four sites were funded in 1995, but due to the high quality of some of the applications not funded, more resources were allocated and an additional four sites funded a few months later. A steering committee was established, consisting of the PI from each project and from the coordinating centre, service users and federal staff. Decisions were discussed and made by consensus where possible, and were otherwise reached by a vote.

All projects were funded by the CMHS, and although each was responsible for developing and implementing its own programme, a condition of this funding was that each site agreed to cooperate in developing a common protocol, sometimes modifying the original study design to do so. Each was able to contribute ideas to the overall study. During the project, additional funding was obtained from the Social Security Administration and other federal sources to develop additional projects covering topics such as service user satisfaction and employer attitudes.

The project found supported employment to be superior to 'usual services' in terms of participants being more likely to gain competitive employment, to work longer hours and to have higher earnings (Cook, et al. 2008). It also highlighted the importance of close integration of vocational and clinical services for increasing participants' likelihood of finding competitive employment.

Using the EIDP data, Razzano et al. (2005) looked at outcomes for subgroups within the population with severe mental illness. Generally, they found that clinical factors such as self-reported functioning, recent hospitalisation and negative psychiatric symptoms were more closely associated with employment outcomes than diagnosis was. They did, however, find that a diagnosis of schizophrenia was associated with a lower likelihood of working for 40 hours or more per month, even once symptoms and functioning were controlled for. Commenting on this finding, Cook et al. (2008) suggest that 'special care should be taken in developing appropriate vocational options and employment opportunities to address the unique needs of those with diagnoses of schizophrenia and other schizophrenia-spectrum disorders.'

Dissemination was funded by the US Department of Education, the National Institute on Disability and Rehabilitation Research, and CMHS/SAMHSA. Early findings were briefed in government forums including the White House Conference on Mental Health in 1999 and a Center for Mental Health sponsored employment summit. Technical assistance was also provided to a number of federal agencies, including the Center for Substance Abuse

Treatment, the Center for Substance Abuse Prevention, NIMH, the National Institute on Disability and Rehabilitation Research, the General Accounting Office, the Social Security Administration, the Department of Labor, and the Department of Veterans Affairs.

The team involved in the project considered the successful collaboration of the various sites involved as critical to its success (Cook, et al. 2002). Carrying out a large, long-term, multisite study required the coordinating centre, steering committee and individual sites to work closely together to overcome logistical difficulties and unexpected challenges (eg two federal government shutdowns occurred during the project), as well as in ensuring validity and reliability across the sites, and in maintaining a focus on the shared aims of the study.

1997: Development of the IPS Fidelity Scale

As the number of IPS programmes in the US increased, a fidelity scale was developed in an attempt to reduce the variability found among the models implemented. It provides clear guidance on which elements of the programmes are critical and how they should best be implemented. Studies on the effectiveness of different models of supported employment had suggested varying outcomes, but differences in programme design and implementation made the reasons for these unclear (Bond, et al. 1997). The scale is able to differentiate between supported employment and non-supported employment, as well as between the IPS model and other models of supported employment.

Bond sees the development of this scale as being one of the critical facilitators for the dissemination and successful implementation of supported employment, in that it provides a simple, clear structure to guide programme development (Bond: Personal Communication, 2011). It was only really after the publication of the scale that use of the specific IPS model became widespread. Up until that point, many of the programmes claiming to be based on it more accurately resembled Danley and Anthony's (1987) Choose-Get-Keep model (eg included an initial pre-employment preparation phase) (Bond: Personal Communication, 2011). Since its initial development, both the original fidelity scale and a more sensitive revised version have demonstrated predictive validity, with higher fidelity associated with better programme outcomes (Bond, et al. 2012).

1998: Robert Wood Johnson Foundation conference

Following the emergence in the 1980s of an emphasis on evidence-based medicine in the mental health field, efforts began to identify which of the range of interventions available were most effective. In 1992 the US Agency for Health Care Policy and Research (AHCPR) and NIMH established the Patient Outcomes Research Team (PORT) for Schizophrenia at the University of Maryland School of Medicine and John Hopkins University School of Public Health, with the aim developing and disseminating recommendations on the treatment of people with schizophrenia. The first full set of recommendations was published in 1998 (Lehman, et al. 1998).

Following their publication, a panel of researchers, clinicians, service users and family advocates was convened by the Robert Wood Johnson Foundation to take this forward by establishing which interventions had the strongest evidence base and to move beyond the findings of the PORT study to encourage their routine implementation (Mueser, et al.

2003). Supported employment was identified as one of six such interventions, the others being collaborative pharmacological treatment, assertive community treatment, family psychoeducation, teaching illness management and recovery skills, and integrated dual disorders treatment for substance abuse and mental illness.

Gary Bond considered this conference to be a landmark event in the development and adoption of supported employment: 'The idea of having employment services had been around for a while, but people said "Yes there are a lot of different models. There is the Club House, there's this, there's that." But it wasn't until 1998 that people were saying it's supported employment per se that we ought to be doing.' (Bond: Personal Communication, 2011).

1998: National Implementing Evidence-Based Practices for Severe Mental Illness Project begins

Following the Robert Wood Johnson Foundation conference, a programme was put in place to promote the dissemination of the six evidence-based practices identified. One of the strategic objectives of the Robert Wood Johnson Foundation at the time was 'improving chronic illness care through the use of evidence-based disease management protocols or algorithms' and the Foundation provided funding (of just over $360,000) for this implementation project through its support of the Texas Medication Algorithm Project, the first attempt to evaluate clinical and economic outcomes associated with algorithm-based care for seriously mentally ill patients treated in a public mental health system.

The Implementing Evidence-Based Practices Project, which was also jointly funded by SAMHSA ($2.1 million), the West Institute ($1.5 million) and Johnson & Johnson ($2.6 million), and with the support of the National Alliance for the Mentally Ill, aimed to develop implementation toolkits to encourage systematic adoption of the interventions. This strategy was based on the observation that simply disseminating practice guidelines alone is not sufficient to change practice and consisted of three stages: (i) developing the toolkits by identifying the critical elements of each intervention and the evidence available for each; (ii) a two-year, multisite pilot study of the toolkits; and (iii) a broad dissemination effort to make the implementation packages and standardised training widely available throughout the US.

For supported employment, 89% of the sites in the study had attained high-fidelity implementation of the programme at the 24-month assessment point, the highest proportion out of the six evidence-based practices included in the project (McHugo, et al. 2007).

The project team also reported a number of lessons they considered valuable in future attempts to implement such programmes (quoted directly from Robert Wood Johnson Foundation, 2008):

1. *In a project such as this one, a range of stakeholders should be involved from the beginning.* Although it is less time-consuming to focus mainly on practitioners, involving all the stakeholders, including consumers, family members and state

mental health authorities, leads to a better product. (Project Team Members/McHugo, Torrey).

2. *Sometimes it is not possible to reach consensus when bringing together groups of stakeholders with different interests.* In those cases, it is important to have people who can manage the politics of the situation, synthesize a range of opinions and make decisions. (Project Team Members/McHugo, Gorman).
3. *The priorities of researchers, policy-makers and the public sometimes are at odds over the question of when to disseminate promising program models.* Early indications of the toolkits' benefits for the seriously mentally ill fed a demand for a national dissemination. SAMHSA responded by funding additional states to implement the evidence-based practices. The Dartmouth researchers feel that national dissemination should wait until their eight-state evaluation, data analysis and subsequent revision of the toolkits is complete in 2006. (Project Director/Drake).
4. *Leadership at all levels plays a crucial role in the effective implementation of evidence-based practices.* According to project director Robert Drake, because of the toolkit field test, 'we now have thousands of experiments across the country, which have proven that in mental health, training by itself is not enough to create change.' (Project Director/Drake).

2000: First Canadian IPS programmes begin to emerge

As in the US, Canada had a long history of vocational rehabilitation programmes, with sheltered work programmes having existed throughout much of the twentieth century. In the 1970s some consumer-run businesses began to emerge (Menear: Personal Communication, 2012), particularly as part of an Ontario movement that emerged quiet independently of US trends, and this period saw growing diversity in the range of vocational services available (Latimer: Personal Communication, 2011). Menear commented that during this time services emerged in response to service user needs that became apparent with the closure of mental hospitals and move towards community care; there was no concerted effort from authorities at the time to implement any particular model (Menear: Personal Communication, 2012). A similar trend in Quebec had seen some early forms of supported employment emerge in the mid-late 1970s (Menear: Personal Communication, 2012). These were set up by community-based not-for-profit organisations, the leaders of which would sometimes attend conferences where some of the US developments were discussed. Many of these organisations subsequently became service providers for the Quebec government in the 1980s, under its *Service externe de main d'oeuvre* programme.

As was the case in the US, it was not until the mid to late 1980s that programmes based on supported employment principles became more common, and by the mid-1990s, a number of vocational rehabilitation agencies in some Canadian provinces were moving towards such programmes as the evidence base in the US grew. The first programmes specifically using the IPS model were launched in 2000.

The first IPS programmes in British Columbia were set up on the back of the research evidence emerging from the US in the late 1990s. Kim Calsaferri, who at the time was

managing rehabilitation services at Vancouver Community Mental Health Services and contracting with multiple non-profit agencies including the Canadian Mental Health Association Vancouver-Burnaby branch (CMHA-VB), was looking at the range of services needed in Vancouver and how the system could support people's citizenship. At the time, the concept of recovery was rapidly gaining prominence in the field. She was aware of the research literature on supported employment, and with the support of a new, forward-thinking Executive Director at CMHA-VB, Jonathan Oldman, made the decision to shift one contracted service using an old sheltered workshop model to IPS instead (Calsaferri: Personal Communication, 2011). The evaluation of this programme suggested that converting sheltered workshops to IPS was both feasible and advantageous (Oldman, et al. 2005).

Calsaferri and Oldman looked at the number of IPS vocational counselors that could be accommodated within the funding envelope, then asked the directors of the eight mental health teams to offer their site if they could meet a set of criteria which would support implementation of fidelity based IPS. Programmes began in three of the teams, with champions of the IPS approach from the US being brought in to provide training and ongoing support. The IPS Advisory Group, worked to develop an implementation manual to guide the establishment of the programmes and emphasised fidelity as an essential aspect. Since this time a fourth team has added IPS following some redesign within the Rehabilitation Services.

Calsaferri suggested that having positive relationships with funding agencies was important in developing the range of supported employment programmes in the catchment area at the time. For example, another supported employment programme, Gastown Vocational Program, received funding from both the Ministry of Health and the Ministry of Social Development, and as the latter had access to education funding, the agency was able to blend supported employment and supported education services to allow younger people to stay in school and gain work experience. Calsaferri identified close collaboration between different stakeholders an important element in maximising the effectiveness of both supported education and supported employment.

> I think, at times of fiscal constraint, different services and also Ministries may dispute whether they are in the business of, say, housing and employment. They may say this is the responsibility of someone other than themselves. However, I know that we would not have IPS if we hadn't had Ministry of Health dollars. What happens is everybody pushes the ball to somebody else's court. I think we could provide better service if we partnered around dollars and effective models for the mental health population, but there has to be a commitment from both to that. What tends to happen is that one funding source, for example, is focused on getting employment outcomes across mainstream society with little focus on people with severe disabilities, such as serious mental illness, and the other group is wondering if we should provide the service at all.
>
> (Calsaferri: Personal Communication, 2011)

Collaboration between agencies may also be important from an advocacy point of view. Calsaferri suggested that one of the barriers to people participating in supported

employment programmes is the fact that joining the workforce will result in loss of benefits:

> Clients are very nervous about giving up their benefits, even though in BC you are supposed to be able to get quickly back on when and if you need. So I think there needs to be some work done […] so that people are very clear that that can happen – and advocacy to make sure it does happen, because I think one of the barriers is also misinformation and some inconsistency in implementation of policy.
>
> (Calsaferri: Personal Communication, 2011)

As crucial as external partnerships were, Calsaferri highlighted the importance of having a good, well-led team within the health authority as well: 'I think you have to have some cheerleaders within the organisation who are prepared to hang in […] After we got this programme in place we met for over two years. I had all the team directors at that table, the CMHA and their Executive Director and the leader of the IPS programme, Leigh Thomson, some of our case managers and other rehabilitation staff of those teams. Everybody was on board and we were problem solving through any of the issues. Everybody was clear about where we were going.' (Calsaferri: Personal Communication, 2011).

In Quebec, it was around this same time that academics with links to US experts in supported employment began working with hospital administrators and providers to implement the province's first IPS programme. Eric Latimer recalled that he first heard of IPS from a colleague (Tania Lecomte) who had just completed a postdoc at UCLA, after they both attended a presentation about the new vocational rehabilitation programme at the hospital where they were based. Lecomte then persuaded the hospital's administration to invite Drake and Becker to give a talk at the hospital in May 2000, and the programme was underway by January 2001.

Latimer suggested that the fact that Dartmouth is not far from Montreal may have been an important enabling factor in launching the first programmes in Quebec, as it was fairly easy for the Dartmouth team to visit to talk about their work. Menear noted that: 'IPS programmes really only emerge in places where people who were implementing the programmes had access to experts… And once you have contact with them then you also have the support for implementation that's so valuable… There are a lot of reasons why they do what they do, and so there's a value system that comes along with it that can get passed on from experts in the US to people here in Canada.' (Menear: Personal Communication, 2012)

Latimer was invited to evaluate the programme's implementation and outcomes, and to do so decided to conduct a randomised controlled trial: the first such study in Canada. After their involvement in the launch of the programme, Becker and Drake helped train IPS staff, a factor which Latimer felt to be particularly important in the success of the programme, and also became co-investigators on the RCT.

As in Quebec and BC, it was not until the mid-1990s that supported employment programmes emerged on any great scale in Ontario. However, unlike in other provinces, where such programmes were established initially through grassroots developments, much

of the initial impetus in Ontario came from the policy level. The Graham Report, as discussed above, had set the scene for reform of community mental health in the late 1980s, but a change of government in 1990 led to this being reviewed and a new strategy formulated. A report was published by the provincial Ministry of Health (Ontario Ministry of Health, 1993) which, in recognition of the failure of previous policies to extensively change practice, was focused much more on implementation, clearly setting out a series of best practices that included supported employment (Menear: Personal Communication, 2012). A similar document, again with a focus on best practice in implementing services, was published a few years later as part of a project set up by the Federal/Provincial/Territorial Advisory Network on Mental Health (ANMH) and Health Canada (Clarke Institute of Psychiatry, 1997). This report, which Menear highlighted as particularly influential in directing provincial policy towards evidence-based supported employment, had a focus on implementing best practices across an entire system of care, emphasising the need for collaboration and the integration of services.

Although the gradual move towards evidence-based community mental health services was gaining momentum in Ontario, political events and shifting priorities hindered these changes to some extent (Menear: Personal Communication, 2012). In particular, the global outbreak of severe acute respiratory syndrome (SARS) in 2002–3 hit Toronto and the province more widely, particularly hard, and necessarily became the primary focus for the Ministry of Health at that time.

> [A] new policy would get drafted and then before you can implement that vision, there's a new party in power. So between the 1980s and mid-2000s you had several parties come to power and put forth a vision, and even though [the visions are] fairly related to each other, you don't have the same people in power necessary to implement them. The intentions were there – they had a very modern vision of how services should be, how the mental health system should be, but they weren't able to put in place that vision.
>
> (Menear: Personal Communication, 2012)

More recently, major changes in the provision of employment services have come about with changes to the policies of the Ontario Disability Support Program, a programme run by the Ministry of Community and Social Services (Menear: Personal Communication, 2012). In its early years (late 1990s to early 2000s), although the aim of the fund was to encourage people to become self-reliant and re-enter the workforce, a number of disincentives existed due to the benefits system and the way the programme operated. Following a change of government, a new version of the programme was launched in 2006 which focused much more on helping people move rapidly into employment and minimising the prevocational preparatory phase. To incentivise this, agencies providing services were paid according to programme outcomes: for example, finding a competitive job, retaining a competitive job for three months, and so on. This new model brought practice much more into line with IPS principles, although without the emphasis on integration of mental health and rehabilitation services.

As the above examples demonstrate, IPS programmes in Canada only emerged once a substantial evidence base had been built up in the US and the programme began being disseminated more widely. Several interviewees commented that they were very aware of

the US literature at the time, and as the IPS model was already well developed, Canadian efforts initially focused far more on implementation of supported employment programmes than on carrying out further studies and trials. 'I would say, in general, the various Canadian provinces have been pretty aware of trends in the United States. Even in Quebec, which is primarily French speaking, it generally has not taken very long for ideas and trends from the United States to become known here and to have some influence.' (Latimer: Personal Communication, 2011).

The nature of funding policy in Canada may also have helped launch some of the early supported employment programmes. In contrast to, for example, the UK, the majority of research in Canada was investigator-driven at the time (Latimer: Personal Communication, 2011) and so researchers were able to focus on areas they saw as promising, obtaining flexible funding for demonstration projects and trials. Additionally, health authorities tended to offer recurrent funding for implementing programmes, with few constraints on programme structure (Menear, et al. 2011). However, part of this flexibility was due to a general belief among health authorities that a variety of programmes should be available to service users, rather than a prescribed approach supporting only those with a strong evidence base. This meant that little was done to actively support dissemination of supported employment, and many health authorities maintained other vocational rehabilitation programmes alongside it. Latimer suggested that together these providers of more traditional services constitute a powerful lobby in opposition to IPS (Latimer: Personal Communication, 2011).

This is not necessarily a bad thing though, according to some interviewees: 'yes, it's important that the people who have the most serious needs have the kind of support that the IPS model provides, yet in other cases people don't necessarily have those kinds of needs […] And so it makes you think that having that sort of diversity in terms of the different types of employment models may be a good thing, because you're preventing people from falling into the cracks, able to actually meet needs on a larger scale.' (Menear: Personal Communication, 2012).

Dissemination of supported employment programmes may also have been limited by the programmes' intersectoral nature. Menear commented that Assertive Community Treatment emerged in Ontario at around the same time as supported employment, but was rolled out much more rapidly, despite both interventions having a similarly strong evidence base: '[Supported employment] affects not just people within the health sector but also people within the employment sector, the community or voluntary sector, education stakeholders are involved, and so as a result there's a whole bunch of people that you have to get on board to be able to roll it out. And that's pretty complicated.' (Menear: Personal Communication, 2012).

Menear commented that there is work going on in Canada to understand the different components of the IPS model in the Canadian context and to look at what may be similar or different to the US. He added: 'I think as Canadian researchers gain that legitimacy as well, they are in a better position to advocate for a different type of model, but it's hard to go against 20 years of research. So I think that we could see down the road a model that's more Canadian – has a Canadian flavour to it.' (Menear: Personal Communication, 2012).

Around 2000: Supported employment begins to emerge in the UK

The growing profile of IPS and the mounting evidence from RCTs of the effectiveness of supported employment began to attract interest outside North America in the late 1990s and early 2000s, including in the UK. Burns first came across supported employment when visiting Dartmouth to look at assertive outreach in 1992, but was not aware of anyone in the UK implementing or researching the topic at that time (Burns: Personal Communication, 2011). Several years later, in the late 1990s, Rachel Perkins, who like Burns was at St George's Hospital in London, visited Dartmouth as part of her work on clubhouse programmes. In doing so, she met Robert Drake and was introduced to the IPS model. When she returned to London, she and Burns set up a similar programme at St George's.

Bond commented that he had presented on IPS at a conference in Belfast in 1998, and although there was interest in his ideas, it appeared to him that social firms (companies with a social mission of providing employment opportunities for disadvantaged people) and sheltered workshops were still the dominant model of vocational rehabilitation being implemented in the UK at the time.

At around the same time, Burns also wrote an application for European Union funding to conduct the first European RCT of IPS programmes. He recalled citing very little research outside the US in the application, and certainly none in the UK (Burns: Personal Communication, 2011). The findings of this study, covering programmes in six countries, were published in 2007 (discussed below).

2001: Cochrane review

By the end of the 1990s supported employment was becoming more widespread – as discussed above, particularly in the US – and a growing number of RCTs had investigated its effectiveness. A Cochrane review was conducted to compare supported employment (in the form of the IPS model) with standard community care and with vocational rehabilitation that focused on a pre-vocational training period (Crowther, et al. 2001). The US-centric development of the evidence base for vocational rehabilitation was reflected in the fact that all but one of the eighteen RCTs included were conducted in the US, the final one being a trial of pre-vocational training carried out in London.

The authors of the review concluded that: 'Supported employment is more effective than Pre-vocational Training in helping severely mentally ill people to obtain competitive employment. There is no clear evidence that Pre-vocational Training is effective.' (Crowther, et al. 2001).

2001: Launch of the Johnson & Johnson – Dartmouth Mental Health Learning Collaborative

By the early 2000s, a substantial evidence base for the effectiveness of supported employment had built up in the US, as demonstrated by the Cochrane review published in 2001. Demonstration projects such as the EIDP and the Implementing Evidence Based Practices project had led to services becoming reasonably well established in a limited number of states, but wider dissemination efforts had yet to be undertaken.

In light of this, the Dartmouth Psychiatric Research Center developed a public-private-academic partnership aimed at improving access to supported employment services and systematically rolling out the standardised IPS programme on a much larger scale. The project began in 2001 as a one-year pilot programme in three states: Connecticut, South Carolina and Vermont. In implementing the programme, state leaders from mental health and vocational rehabilitation authorities selected appropriate sites and the Dartmouth team provided training and technical assistance. After it was established that employment outcomes were positive at the pilot sites (Becker, et al. 2011) the programme has gradually expanded to the extent that as of early 2012 there are over 130 programme sites across 12 states plus the District of Columbia.

The programme in each state is funded through a series of four one-year grants. In the first year, funding is from the Johnson & Johnson Office of Corporate Contributions and is matched by contributions from the state-level departments of mental health and vocational rehabilitation. Over the subsequent three years, the state assumes greater responsibility for funding the programme.

Although direct funding ends after four years, the collaborative aspects of the project remain in place, with states encouraged to continue meeting, sharing outcome data and materials, and access ongoing support from the Dartmouth team. This learning collaborative approach is not common in the field of mental health, but is similar to the approach used by NIMH in the 1970s to disseminate the Community Support Program (Becker, et al. 2011).

The programme allowed the Dartmouth team to roll out the IPS model in a controlled and systematic way, ensuring that each site had the training and support necessary to replicate the programme with high fidelity. Bond commented: 'It was really, in my view, the work of the Johnson and Johnson Learning Collaborative that really started the systematic dissemination of a model with some kind of integrity.' (Bond: Personal Communication, 2011).

Bond et al. (2011) highlight that while dissemination of the IPS model in a highly systematic, planned way has taken place in the US, this has not been the case in Canada, despite systematic monitoring of clearly defined standards being necessary to ensure fidelity.

2001–3: President's New Freedom Commission on Mental Health Report published in the US

Building on the disability legislation put in place in the previous two decades, President Bush launched the New Freedom Initiative in February 2001. This was designed to promote full access to community living for people with disabilities, including the provision of education and employment opportunities. Of particular influence in the design of the initiative was a landmark decision in the US Supreme Court that ruled that the institutionalisation of a person with a disability who, with appropriate support, is able to live in the community is discrimination under the Americans with Disabilities Act ('Olmstead v L. C.' 1999). Federal agencies were directed to work with States to ensure accessibility of community services, a process which identified a number of barriers in their policies, programmes, regulations and statutes. Priorities and steps to take action were

developed and in April 2002 the president established the New Freedom Commission on Mental Health to carry out a comprehensive study of the gaps in the mental health service system. The Commission was also tasked with making recommendations for improvements to be made by Federal government, State governments, local agencies and public and private healthcare providers.

The Commission's final report, published in 2003, incorporated the views of 2,300 mental health consumers, family members, providers, administrators, researchers, government officials, and other key stakeholders in making recommendations to overcome the barriers posed by: (i) stigma around mental disorders; (ii) the treatment limitations and financial requirements placed on mental health benefits by private medical insurance; and (iii) the fragmented mental health service delivery system (New Freedom Commission on Mental Health, 2003).

With a focus on the concept of recovery, and emphasis on the fact that many evidence-based practices were not widely available, the Commission set six goals for transformed mental health services in the United States:

1. Americans understand that mental health is essential to overall health.
2. Mental health care is consumer and family driven.
3. Disparities in mental health services are eliminated.
4. Early mental health screening, assessment, and referral to services are common practice.
5. Excellent mental health care is delivered and research is accelerated.
6. Technology is used to access mental health care and information.

Under the fifth of these goals, the Commission endorsed the National Implementing Evidence-Based Practices Project, in which supported employment was one of the targeted interventions, as well as including a specific recommendation to 'advance evidence-based practices using dissemination and demonstration projects and create a public-private partnership to guide their implementation'. This was subsequently taken forward by SAMHSA as they created an action agenda to implement the Commission's Recommendations in collaboration with other federal, state and local level organisations (SAMHSA, 2005).

2004–7: UK government endorses IPS and encourages its implementation through a number of reports and pieces of legislation

Since the election of the UK Labour government in 1997, the *Welfare to Work* agenda had been a driving force in setting the direction of UK employment and welfare policies (Schneider, et al. 2007). This programme focused on reducing the number of working age people claiming social security benefits, with one target group being the disabled. Revisions to the Disability Discrimination Act in 2000 and 2005 set out the rights of disabled people in employment and specified employers' obligations in relation to equal opportunities. In particular, the 2005 amendments widened the definition of mental health to include many more people with mental health problems.

As IPS programmes became more widespread in the US, the UK government began advocating for their implementation for those with mental health problems. A report published by the Social Exclusion Unit in the Office of the Deputy Prime Minister listed IPS as one of six models of vocational rehabilitation in use, but did also note that there was substantial evidence of its superiority over other models in terms of its effectiveness in enabling people with severe mental health problems to work (Social Exclusion Unit, 2004). The report also noted that a cost-effectiveness study commissioned by the Social Exclusion Unit found supported employment and specifically IPS to be significantly more effective than other approaches, and that the conversion of less effective programmes to supported employment could be cost-saving, or at least cost-neutral, for local services and the government.

Around the same time a Department of Health report, *Choose health: Making healthy choices easier*, committed to working with the Department of Work and Pensions in implementing evidence-based vocational rehabilitation programmes, and in particular IPS (Department of Health, 2004). The report recommended that vocational and social support be embedded in care plans, in partnership with local organisations including Jobcentre Plus and education providers.

A Green Paper from the Department for Work and Pensions followed in 2006, setting out a ten-year programme aiming to reduce the number of people claiming incapacity benefit by introducing vocational advisers in GP surgeries and creating partnerships between health services, employment services and local authorities, while also imposing a stricter benefits environment (Schneider, et al. 2007). Commissioning guidance in line with this, jointly developed by the Department of Health and the Department for Work and Pensions, followed in the same year, and in 2007 the government set a related target in the national Public Service Agreement (PSA) as a key priority outcome for the period 2008–2011. Specifically, PSA 16 aimed to increase the proportion of socially-excluded adults in settled housing and in full-time employment, education or training, with one of the four targeted groups being adults in contact with secondary mental health services (HM Treasury, 2007).

2006: First Canadian RCT of IPS model

As discussed above, the first RCT of supported employment conducted in Canada looked at the programme implemented in Quebec with the support of Becker and Drake. In a study funded by CIHR, FRSQ and the Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé (AETMIS, the Québec government agency responsible for health services and technology assessment Latimer et al. (2006) compared a group assigned to an IPS programme with a group receiving services as usual. At follow up after one year, the IPS group demonstrated significantly better employment outcomes than the control group, providing evidence that IPS can be effectively implemented in a context very different to that of the US. Despite this, the authors noted that there was still a significant proportion of clients (53%) in the IPS condition who were unable to obtain any competitive employment during the first year, suggesting that there was still value in exploring potential enhancements to the model.

2007: SESAMI study in the UK publishes first findings

Acknowledging that substantial evidence had been built up from randomised controlled trials in the US, a UK group decided to look at how people with mental health problems were being supported to get and keep work in a real life setting in the UK. They noted that employment support was available from a wide range of sources in the UK, with programmes delivered through employment services, generic disability services and specific mental health agencies. The SESAMI (Social inclusion through Employment Support for Adults with Mental Illness) study, funded by the European Social Fund, involved a series of case studies of agencies providing employment support, including the Department for Work and Pensions, a mental health trust, a private business and three voluntary organisations (Schneider, et al. 2007; Schneider, et al. 2009).

The initial findings across the six programmes studied indicated that:

- provision was dominated by models funded by government programmes for disabled people in general, not specifically tailored to mental health;
- most beneficiaries were men, as is often found in studies of employment interventions;
- those in work were doing a wide range of jobs;
- most people with severe mental health problems 'on the books' of these programmes were in pre-work situations.

A follow up twelve months later looked at outcomes for the people enrolled in the six programmes (Schneider, et al. 2009). As well as generally demonstrating the benefits of working for people with mental health problems, the findings also lent support to the IPS model of supported employment, emphasising the importance of a rapid job search and integration of employment and mental health services.

2007: EQOLISE: the first European RCT of IPS model

The first European RCT of IPS was published in 2007 (Burns, et al. 2007). It looked at the effectiveness of IPS programmes in six European countries with varying labour markets and welfare systems (the UK, Germany, Italy, Switzerland, Netherlands and Bulgaria), using as a control group the best available local alternative vocational service.

Overall, the IPS programmes were found to be more effective than the control vocational services: the rate of obtaining competitive employment was twice as high, patients kept their job for longer and the mean number of hours worked was greater. The high employment rate did not appear to have a detrimental effect on clinical wellbeing, as there was actually a reduced rate of hospital readmission among the IPS group, something not previously found in US studies. The authors speculate that this may be due to the generally greater integration of health and social care in Europe.

However, the study did find some effect of socioeconomic context. Generally, more patients obtained jobs when the country's economy was growing. In particular, local unemployment rate seemed important: the sites in Bulgaria and Italy, which had the most successful IPS services, were also the two at which the local unemployment rate was much lower than the rate nationally. This buoyant local economy appeared to make it easier for IPS workers to find unskilled positions for individuals with severe mental illness.

Programmes were also more successful where social exclusion was more marked, possibly because these countries offered less welfare support. Similarly, it also appeared that where a country's welfare system created a financial disincentive to finding competitive employment (ie a 'benefit trap'), this may have been a barrier to programme success.

Burns commented that he sees the benefit trap as a particular challenge to operating a successful IPS programme in the UK: 'To be honest, there is no financial incentive to work for many of our patients at all, whereas, if you go to America it's so stark – the benefits are so meagre – that any work helps. One of the nice things about our European study is we had two countries which have a large black market, Bulgaria and Italy, and they did fantastically well because they don't have a benefit trap. They have low benefits, but if you earn a bit of money, nobody's going to come snooping around and saying, "We're going to cut your benefits."' (Burns: Personal Communication, 2011)

2009: UK government publishes a series of related policy documents in support of IPS

Despite the UK government's growing endorsement of supported employment from 2004 onwards, Rinaldi et al. (2010) reported that, according to the Information Centre for Health and Social Care, only 3.4% of UK adults in contact with secondary mental health services with an enhanced level of care planning were known to be in paid employment in 2009.

Burns commented that although various government documents had endorsed supported employment, there have been very few changes in legislation to support its adoption, adding 'we've been lobbying for a change but we've not succeeded in getting one […] that endorsement is extraordinarily hollow' (Burns: Personal Communication, 2011).

A number of barriers may exist to adoption of supported employment, and IPS specifically, in the UK. Burns noted that in many places stepwise models of vocational rehabilitation are still in use, possibly due in part to cultural differences between the UK and the US, and the fact that implementing agencies in the UK may be less likely to readily adopt 'franchised models' such as IPS (Burns: Personal Communication, 2011). Additionally, many of the policies and programmes introduced under *Welfare to Work* were not specific to people with mental health problems, instead broadly targeting disability benefit claimants. Dickens et al. (2004) reported that advisors on the government's *Pathways to Work* initiative found mental health issues the most challenging cases and sometimes deferred work opportunities on the grounds of mental illness, partly due to anxiety or lack of confidence of the advisors in working with this group.

Burns commented that implementing a new intervention can also challenge staff by being quite disruptive to existing practices and not necessarily always appearing at first to be in a patient's best interest: 'It's the good staff who oppose you, not the bad staff. Good staff know their patient very well, have seen them through terrible times, and want to protect them. So I think one of the barriers is that it cuts right across many of the fundamental principles of good therapeutic relationships, ie protecting your patient, bearing in mind their history, all that sort of stuff [...] I think one should not underestimate how at variance it is to normal practice in mental health.' (Burns: Personal Communication, 2011). Burns also commented that outcomes are relatively distant and probabilistic in nature, requiring

persistent commitment from the therapist: 'So for instance, if you're doing something that is quite demanding of you but you can see the results in front of your eyes, then that's okay. You can't see the results in front of your eyes with IPS because all you're doing is increasing the likelihood of somebody getting a job in the next year from 20% to 50% [...] it's very hard to stay focused on that when you've got another patient who's crying and needs support, where you can actually immediately see the benefit of input.' (Burns: Personal Communication, 2011).

Supported employment programmes are also based on the assumption that the people they are targeting actually want to work, and Burns highlighted that this might not always be the case: 'But of course it's very difficult to say to somebody, "Wouldn't you like to work?" and them to say, "No." I mean it's socially unacceptable to say no.' (Burns: Personal Communication, 2011).

In response to some of the challenges faced, the UK government published a series of related policy documents advocating the IPS approach. These included an independent review on how people with mental health conditions can better be supported into employment (Perkins, et al. 2009), a new mental health strategy (HM Government, 2009a), a national strategy for mental health and employment (Department of Work and Pensions and Department of Health, 2009) and a response to the Perkins Review setting out actions to support people in secondary mental health services (HM Government, 2009b).

2010–11: The Supported Work and Needs (SWAN) study casts doubt on the effectiveness of IPS in the UK

Following the suggestion from the EQOLISE findings that barriers to successful implementation of IPS programmes might vary by country, the first UK-specific RCT was undertaken at the Institute of Psychiatry in London (Howard, et al. 2010). The study compared groups of people with severe mental illness in either an IPS programme or treatment as usual. Unlike in the majority of previous RCTs internationally, follow up at one year showed no significant difference between the two groups in achievement of competitive employment. The authors suggest a number of potential reasons for this, including economic disincentives affecting the labour market, low levels of motivation to find competitive employment, the relatively high proportion of participants from ethnic groups other than 'White' and aspects of the IPS programme administration, in particular, its lack of integration with community mental health services. Burns agreed that the programme was poorly implemented, and that despite its apparent high fidelity to IPS principles (as measured by the Fidelity Scale), features such as the amount of contact participants had with employment consultants may have been suboptimal. This was also highlighted in a commentary by Latimer, in which he made the observation that clients had contact with IPS workers just over once per month on average, something reflected in the programme's very low cost in comparison to other successful IPS programmes (Latimer, 2010). Latimer also commented that the outcomes of the SWAN study draw attention to the limitations of scales such as that used to measure IPS fidelity.

A two-year follow up showed some improvement in the IPS group, with participants in this intervention significantly more likely to have gained competitive employment (Heslin,

et al. 2011). However, outcomes were still poor in comparison to previous (non-UK) RCTs of IPS programmes. While noting the weaknesses in the approach discussed above, the authors suggest that by being conducted in a 'real world' setting, the study is valuable in highlighting some of the difficulties of implementing vocational interventions in the UK for the most severely mentally ill groups.

Supported Employment

1970

1970 Instant Placement model (Newman) Rehab for community MH

Late 1940s Club house movement founded on the premise that work is important and that clubhouses can provide a stepping stone to competitive employment

1975

1974 PACT model (training in community living program initially) (Stein & Test, 1980; Stein, et al., 1975)

1970s Vocational Rehab services begin to become readily accessible to people with psychiatric disabilities, through the 1973 Rehabilitation Act (establishing the RSA), through NIMH establishing the Community Support Program, and for veterans through the VA's Compensated Work Therapy Program. (Pratt et al., 07)

Mid-late 1970s Need for better community services leads to the emergence of some consumer-run business in Ontario and early forms of community-based supported employment in Quebec

1978 NIMH and RSA establish two vocational rehab research and training centres

Ineffectiveness of led to

1980

1980 NIMH, RSA, the National Institute on Handicapped Research and Council of State Administrators of Vocational Rehabilitation enter into a cooperative agreement

1981 Conference: Improving interagency collaboration between vocational rehabilitation and mental health agencies

IPS borrows concept of integrated rehabilitation and treatment approach

1984 Interagency work group set up to improve services to the "chronically mentally ill"

1984 Developmental Disabilities Assistance and Bill of Rights Act – growing dissatisfaction and unemployment (see Mank, 1994)

1984 Madeline Will (US Office of Special Education and Rehabilitative Services) proposed model for transition of youths with disabilities from school to work

1984 US Department of Health and Human Services reports that 90,000 developmentally disabled students leave school each year without adequate services or jobs

1980s Workshop approaches to employment shown to be unsuccessful

Evidence growing of ability of people with severe developmental disabilities to live and work successfully in community

1985

1985 SE developed for developmental disabilities (Wehman & Kregel, 1985)

Got SE included in

1986 Amendments to Rehabilitation Act introduced SE as an "eligible service option for persons with severe handicaps"

1986 Wehman model for physical disability

1987 SE adapted for psychiatric rehabilitation - Choose-Get-Keep model (Danley & Anthony, 1987)

1987 Special issue of Psych Rehab Journal

1988 Graham Report in Ontario draws on ideas of consumer/survivor movement to call for vocational support, including SE

1990

IPS takes idea of emphasising client preference

IPS draws on minimizing prevoc training

Consumer choice important

Client preference important

Recovery movement influenced

1) Consumer movement gathers pace
See CH2 of Becker & Drake (2003)

2) Growing emphasis in the medical field on helping patients make informed choices by providing info about options (Wennberg, 1988; Cook, 1992)

3) Recovery movement emphasise sd individual's role in defining improvements in their lives.

4) Psychosocial Rehabilitation perspective gained prominence (originating in US but reaching more widely) – emphasised individual strengths and potential, and stressed power of work as a re-integrative force. (see Menear et al, 11)

1993 Individual Placement and Support model
Becker and Drake, 1993

1995

1995 36,000 people with mental illness now employed in SE positions

1994 Start of RCTs of IPS

Influenced

Mid 1990s Some Canadian vocational rehabilitation agencies move towards implementing supported employment, often gradually

1995 Employment Intervention Demonstration Program funded by SAMHSA

First European trial

1997 New government re-emphasises 'welfare to work' and aims to foster employment opportunities for disabled people

1997 Fidelity scale developed to measure adherence to programme standards and provide operational definitions for key ingredients (Bond et al., 1997) – aimed to prevent model diffusion

Provided evidence

1998 RWJ Conference identifies SE as one of six EBPs in mental health

Led to

2000

1998 Implementing Evidence-Based Practices Project begins (see Mueser et al, 2003)

2001 Johnson & Johnson – Dartmouth Community Mental Health Program begins with 3 site pilot

Early 2000s First IPS programmes emerged in Canada

2000 Cochrane review – SE superior to pre-vocational rehabilitation

2003 New Freedom Report

Inspired

2004 VA Comprehensive Mental Health Strategic Plan – expansion of SE within VA

2004 Social Exclusion Unit endorses IPS in the UK

2005

2005 Disability Discrimination Act – definition of MH changed to cover more people

2005 onwards. EIDP publishes first findings

Demonstrated feasibility and built evidence base in US

2006 First Canadian RCT of IPS published

2006 DH endorses IPS in commissioning guidelines

2006 Government's Social Exclusion Task Force endorses IPS in action plan

2006 DWP Green Paper 'A new deal for welfare: empowering people to work'

2007 First European RCT, EQOLISE, shows applicability in Europe, but also relationship between success and economic disincentives

2007 PSA target 16 to increase the proportion of adults in Contact with secondary mental health services in employment, education or training

2007 Results of SESAMI study published, making recommendations for UK

2008 Only 2% of target population in US have access to evidence-based employment services (SAMHSA, 2009)

2008 Mental Health Treatment Study (Frey et al, 2008)

2009 Government publishes a series of documents stating that IPS should be used in mental health services

2010 SWAN RCT casts doubt on effectiveness of IPS in the UK, but flaws in its methodology are highlighted

2010

USA
Canada
UK
Other

2.5 References

Anthony, W., and Blanch, A. (1987). 'Supported employment for persons who are psychiatrically disabled: an historical and conceptual perspective.' *Psychosocial Rehabilitation Journal* 11(2), 5–23.

Anthony, W. A., Cohen, M. R., and Vitalo, R. (1978). 'The measurement of rehabilitation outcome.' *Schizophrenia Bulletin* (4), 365–383.

Anthony, W. A., and Dion, G. (1986). *Psychiatric Rehabilitation: a rehabilitation research review*. Washington, D.C.: National Rehabilitation Information Center.

Bailey, E. L., Ricketts, S. K., Becker, D. R., Xie, H., and Drake, R. E. (1998). 'Do long-term day treatment clients benefit from supported employment?' *Psychiatric Rehabilitation Journal,* 22(1), 24–29.

Becker, D. R., and Drake, R. E. (1993). *A Working Life: the individual placement and support (IPS) program*. Concord, NH: Dartmouth Psychiatric Research Center.

Becker, D. R., and Drake, R. E. (2003). *A working life for people with severe mental illness.* Oxford: Oxford University Press.

Becker, D. R., Drake, R. E., Bond, G. R., Nawaz, S., Haslett, W. R., and Martinez, R. A. (2011). Best Practices: a national mental health learning collaborative on supported employment. *Psychiatric Services,* 62(7), 704–706.

Bellamy, G. T., Rhodes, L. E., Bourbeau, P. E., and Mank, D. M. (1986). 'Mental retardation services in sheltered workshops and day activity programs: consumer benefits and policy alternatives.' In F. R. Rusch, ed., *Competitive Employment Issues and Answers*. Baltimore: Paul H. Brookes.

Bond, G. R. (1992). 'Vocational Rehabilitation.' In R. P. Liberman, ed., *Handbook of Psychiatric Rehabilitation*. New York: Macmillan, 244–275.

Bond, G. R. (1998). 'Principles of the Individual Placement and Support model: empirical support.' *Psychiatric Rehabilitation Journal* 22(1), 11–23.

Bond, G. R., Becker, D. R., Drake, R. E., Rapp, C. A., Meisler, N., Lehman, A. F., et al., (2001). 'Implementing Supported Employmentas an Evidence-Based Practice.' *Psychiatric Services* 52(3), 313–322.

Bond, G. R., and Dincin, J. (1986). 'Accelerating Entry into Transitional Employment in a Psychosocial Rehabilitation Agency.' [doi: 10.1037/h0091540]. *Rehabilitation Psychology* 31(3), 143–155.

Bond, G. R., Drake, R. E., and Becker, D. R. (2008). 'An Update on Randomized Controlled Trials of Evidence-Based Supported Employment.' *Psychiatric Rehabilitation Journal* 31(4), 280–290.

Bond, G. R., Drake, R. E., and Becker, D. R. (2011). 'Implementation of IPS supported employment around the world: planned vs. unplanned dissemination. A commentary on Menear et al.' [doi: 10.1016/j.socscimed.2011.02.003]. *Social Science and Medicine* 72(7), 1036–1038.

Bond, G. R., Personal Comunication, 2011.

Bond, G. R., Peterson, A. E., Becker, D. R., and Drake, R. E. (2012). 'Validation of the Revised Individual Placement and Support Fidelity Scale (IPS-25).' *Psychiatric Services* 63(8), 758–763.

Burns, T., Catty, J., Becker, T., Drake, R. E., Fioritti, A., Knapp, M., et al., (2007). 'The effectiveness of supported employment for people with severe mental illness: a randomised controlled trial.' *The Lancet* 370(9593), 1146–1152.

Burns, T., Personal Comunication, 2011.

Calsaferri, K., Personal Comunication, 2011.

Clarke Institute of Psychiatry. (1997). *Best practices in mental health reform: Discussion paper*. Ottawa.

Cook, J. A., Blyler, C. R., Leff, H. S., McFarlane, W. R., Goldberg, R. W., Gold, P. B., et al., (2008). 'The Employment Intervention Demonstration Program: major findings and policy implications.' *Psychiatric Rehabilitation Journal* 31(4), 291–295.

Cook, J. A., Carey, M. A., Razzano, L. A., Burke, J., and Blyler, C. R. (2002). 'The Pioneer: the employment intervention demonstration program.' *New Directions for Evaluation* 2002(94), 31–44.

Cook, J. A., Leff, H. S., Blyler, C. R., Gold, P. B., Goldberg, R. W., Mueser, K. T., et al., (2005). 'Results of a Multisite Randomized Trial of Supported Employment Interventions for Individuals With Severe Mental Illness.' *Archives of General Psychiatry* 62(5), 505–512.

Crowther, R., Marshall, M., Bond, G., and Huxley, P. (2001). 'Vocational rehabilitation for people with severe mental illness.' *Cochrane Database of Systematic Reviews*(2), CD003080.

Danley, K. S., and Anthony, W. A. (1987). 'The Choose-Get-Keep Model.' *American Rehabilitation* 13(4), 6–9; 27–29.

Dellario, D. J. (1985). 'The relationship between mental health, vocational rehabilitation interagency functioning, and outcome of psychiatrically disabled persons.' *Rehabilitation Counseling Bulletin* 28(3), 167–170.

Department of Health (2004). *Choose Health: making healthy choices easier*. London: Department of Health.

Department of Work and Pensions, and Department of Health. (2009). *Working our Way to Better Mental Health: a framework for action*. Norwich, UK: The Stationery Office.

Dew, D. W., and Alan, G. M., eds., (2005). *Innovative Methods for Providing VR Services to Individuals with Psychiatric Disabilities (Institute on Rehabilitation Issues Monograph No. 30)*. Washington, DC: The George Washington University, Center for Rehabilitation Counseling Research and Education.

Dickens, S., Mowlam, A., and Woodfield, K. (2004). *Incapacity Benefit Reforms – the personal adviser role and practices* (Prepared for the Department for Work and Pensions). London: NatCen.

Dincin, J., and Witheridge, T. F. (1982). Psychiatric rehabilitation as a deterrent to recidivism. *Hospital and Community Psychiatry* 33(8), 645–650.

Drake, R., Becker, D., Biesanz, J., Torrey, W., McHugo, G., and Wyzik, P. (1994). 'Rehabilitative day treatment vs. supported employment: I. Vocational outcomes.' *Community Mental Health Journal* 30(5), 519–532.

Drake, R. E., Becker, D. R., Bond, G. R., and Mueser, K. T. (2003). 'A process analysis of integrated and non-integrated approaches to supported employment.' *Journal of Vocational Rehabilitation* 18(1), 51–58.

Drake, R. E., Bond, G. R., and Becker, D. R. (2012). *IPS Supported Employment: an evidence-based approach to supported employment.* New York: Oxford University Press.

Drake, R. E., McHugo, G. J., Bebout, R. R., Becker, D. R., Harris, M., Bond, G. R., et al., (1999). 'A Randomized Clinical Trial of Supported Employment for Inner-city Patients With Severe Mental Disorders.' *Archives of General Psychiatry* 56(7), 627–633.

Drake, R. E., McHugo, G. J., Becker, D. R., Anthony, W. A., and Clark, R. E. (1996). 'The New Hampshire study of supported employment for people with severe mental illness.' *Journal of Consulting and Clinical Psychology* 64(2), 391–399.

Farkas, M. D., Rogers, S. E., and Thurer, S. (1987). 'Rehabilitation outcome of long-term hospital patients left behind by deinstitutionalization.' *Hospital and Community Psychiatry* 38(8), 864–870.

Heslin, M., Howard, L., Leese, M., McCrone, P., Rice, C., Jarrett, M., et al., (2011). 'Randomized controlled trial of supported employment in England: 2 year follow-up of the Supported Work and Needs (SWAN) study.' *World Psychiatry* 10(2), 132–137.

HM Government. (2009a). *New Horizons: a shared vision for mental health*. London: Department of Health.

HM Government. (2009b). *Work, Recovery and Inclusion: employment support for people in contact with secondary care mental health services*. London: National Mental Health Development Unit.

HM Treasury. (2007). *PSA Delivery Agreement 16: increase the proportion of socially excluded adults in settled accommodation and employment, education or training.* London: HM Treasury.

Howard, L. M., Heslin, M., Leese, M., McCrone, P., Rice, C., Jarrett, M., et al., (2010). 'Supported Employment: randomised controlled trial.' *The British Journal of Psychiatry* 196(5), 404–411.

Latimer, E. (2010). 'An effective intervention delivered at sub-therapeutic dose becomes an ineffective intervention.' *British Journal of Psychiatry* 196, 341–342.

Latimer, E. A., Lecomte, T., Becker, D. R., Drake, R. E., Duclos, I., Piat, M., et al., (2006). 'Generalisability of the Individual Placement and Support Model of Supported Employment: results of a Canadian randomised controlled trial. *The British Journal of Psychiatry* 189(1), 65–73.

Latimer, E., Personal Comunication, 2011.

Lehman, A. F., Goldberg, R., Dixon, L. B., McNary, S., Postrado, L., Hackman, A., et al., (2002). 'Improving Employment Outcomes for Persons With Severe Mental Illnesses.' *Archives of General Psychiatry* 59(2), 165–172.

Lehman, A. F., Steinwachs, D. M., and The Co-Investigators of the PORT Project. (1998). 'Translating Research Into Practice: The Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations. *Schizophrenia Bulletin* 24(1), 1–10.

Marrone, J. (1993). 'Creating positive vocational outcomes for people with severe mental illness.' *Psychosocial Rehabilitation Journal* 17(2), 43–62.

McHugo, G. J., Drake, R. E., Whitley, R., Bond, G. R., Campbell, K., Rapp, C. A., et al., (2007). 'Fidelity outcomes in the national implementing evidence-based practices

project.' [doi:10.1176/appi.ps.58.10.1279] *Psychiatric Services* 58(10), 1279–1284.

Menear, M., Reinharz, D., Corbière, M., Houle, N., Lanctôt, N., Goering, P., et al., (2011). 'Organizational analysis of Canadian supported employment programs for people with psychiatric disabilities.' [doi: 10.1016/j.socscimed.2011.02.005] *Social Science and Medicine* 72(7), 1028–1035.

Menear, M., Personal Comunication, 2012.

New Freedom Commission on Mental Health. (2003). *Achieving the Promise: transforming mental health care in america. Final report.* (No. DHHS Pub. SMA-03-3832). Rockville, MD.

Newman, L. (1970). 'Instant Placement: a new model for providing rehabilitation services within a community mental health program.' *Community Mental Health Journal* 6(5), 401–410.

Nixon, R. (1973). 'Statement on Signing the Rehabilitation Act of 1973.' As of 20 October 2013:
http://www.presidency.ucsb.edu/ws/?pid=3979

Oldman, J., Thomson, L., Calsaferri, K., Luke, A., and Bond, G. R. (2005). 'A case report of the conversion of sheltered employment to evidence-based supported employment in Canada.' *Psychiatric Services* 56(11), 1436–1440.

Olmstead v. L.C., 527 581 (US Supreme Court 1999).

Ontario Ministry of Health. (1988). *Building Community Support for People: a plan for mental health in Ontario*. Toronto: Ontario Ministry of Health.

Ontario Ministry of Health. (1993). *Putting People First. the reform of mental health services in Ontario*. Toronto: Ministry of Health.

Perkins, R., Farmer, P., and Litchfield, P. (2009). *Realising ambitions: Better employment support for people with a mental health condition*. London: Department for Work and Pensions.

Pratt, C. W., Gill, K. J., and Barrett, N. M. (2007). *Psychiatric Rehabilitation*: Elsevier/Academic Press.

Razzano, L. A., Cook, J. A., Burke-Miller, J. K., Mueser, K. T., Pickett-Schenk, S. A., Grey, D. D., et al., (2005). 'Clinical Factors Associated with Employment among People with Severe Mental Illness: findings from the employment intervention demonstration program.' *Journal of Nervous and Mental Disease* 193(11), 705–713.

Rinaldi, M., Miller, L., and Perkins, R. (2010). 'Implementing the individual placement and support (IPS) approach for people with mental health conditions in England.' *International Review of Psychiatry* 22(2) 163–172.

Robert Wood Johnson Foundation. (2008). *Project Identifies Mental Health Best Practices, Creates 'Toolkits' to Help Implement Them* (Program results report). As of 20 October 2013:
http://www.rwjf.org/reports/grr/044030.htm

Rogers, E. S., Anthony, W. A., and Danley, K. S. (1989). 'The impact of interagency collaboration on system and client outcomes.' *Rehabilitation Counseling Bulletin* 33(2), 100–109.

Rusch, F. R., and Hughes, C. (1989). 'Overview of supported employment.' *Journal of Applied Behavior Analysis* 22(4), 351–363.

SAMHSA. (2005). 'Transforming Mental Health Care in America.' The Federal Action Agenda: First Steps.

Schneider, J., Secker, J., Grove, B., Floyd, M., Slade, J., Boyce, M., et al., (2007). 'The SESAMI Evaluation of Employment Support in the UK: background and baseline data.' *Journal of Mental Health* 16(3), 375–387.

Schneider, J., Slade, J., Secker, J., Rinaldi, M., Boyce, M., Johnson, R., et al., (2009). 'SESAMI* study of employment support for people with severe mental health problems: 12-month outcomes.' *Health and Social Care in the Community* 17(2), 151–158.

Sealy, P., and Whitehead, P. C. (2004). 'Forty Years of Deinstitutionalization of Psychiatric Services in Canada: an empirical assessment.' *Canadian Journal of Psychiatry* 49(4), 249–257.

Social Exclusion Unit. (2004). *Mental Health and Social Exclusion*. London: The Office of the Deputy Prime Minister.

Spaniol, L., Jung, H., Zipple, T., and Fitzgerald, S. (1984). *Needs and Coping Strengths of Families of the Mentally Ill: report of a national survey*. Boston, MA: Center for Psychiatric Rehabilitation, Boston University.

Stein, L. I., and Test, M. A. (1980). 'Alternative to Mental Hospital Treatment: I. Conceptual Model, Treatment Program, and Clinical Evaluation.' *Archives of General Psychiatry* 37(4), 392–397.

Stein, L. I., Test, M. A., and Marx, A. J. (1975). 'Alternative to the Hospital: a controlled study. *The American Journal of Psychiatry* 132(5), 517–522.

Torrey, W. C., Becker, D. R., and Drake, R. E. (1995). 'Rehabilitative day treatment vs. supported employment: II. Consumer, family and staff reactions to a program change.' *Psychosocial Rehabilitation Journal* 18(3), 67–75.

Wehman, P. (1986). 'Supported competitive employment for persons with severe disabilities.' *Journal of Applied Rehabilitation Counseling* 17(4), 24–29.

Wennberg, J. E. (1988). 'Improving the medical decision-making process.' *Health Affairs* 7(1), 99–106.

Will, M. (1984). *OSERS Programming for the Transition of Youth with Disabilities: bridges from school to working life*. Paper presented at the Symposium on employment for citizens who are mentally retarded.

CHAPTER 3 Cognitive behavioural therapy

3.1 Summary

Antipsychotic medication has formed the basis of treatment for schizophrenia since the first antipsychotic drug was developed in 1952. Although antipsychotic drugs have brought considerable benefits to many patients with schizophrenia, they have rarely been associated with complete recovery or full remission of the symptoms of schizophrenia. The reasons for this include the limited efficacy of antipsychotic medication in a substantial proportion of patients (Turkington et al. 2006);[3] the problem of side-effects which some patients experience; and the unwillingness of some patients to take antipsychotic medication (Conley and Kelly, 2001).

The recognition of the limitations of antipsychotic drugs in the treatment of schizophrenia prompted the search for psychosocial approaches that might improve patient outcomes. In the UK increasing numbers of mental health professionals became interested in adapting cognitive approaches and behavioural theory to the treatment of schizophrenia, while in the US there was a focus on strategies grounded in cognitive/behavioural theory to help patients better manage and cope with their illness (Mueser et al., 2002). The original form of cognitive behavioural therapy (CBT), rational emotive behaviour therapy, was developed in the 1960s by Albert Ellis to treat neuroses, but the model of CBT that is most commonly practised today has its origins in the work of A. T. Beck. CBT as a treatment for schizophrenia is part of a wider framework of CBT approaches applied to a range of mental disorders such as anxiety, post-traumatic stress disorder, and depression (Tai and Turkington, 2009). Cognitive theory is based on the notion that the cognitive processes implicated in mood and anxiety disorders occur transdiagnostically, meaning they co-occur across the psychiatric disorders (Harvey et al., 2004). A number of studies have supported the notion that psychotic symptoms can be understood in relation to normal psychological processes and, as a result, the symptoms can be effectively treated by CBT techniques (Yusupoff and Tarrier).

The research base and clinical use of CBT for schizophrenia has developed dramatically over the last ten years as the evidence base for its efficacy has been established by a number

[3] According to Turkington et al., even when patients with schizophrenia fully adhere to antipsychotic medication regimes, up to 50% will have ongoing positive or negative symptoms, with 20-30% of people with chronic schizophrenia demonstrating very little symptomatic response to adequate trials of conventional antipsychotic medications.

of studies[4] and CBT has been endorsed in national guidelines in the US, Canada and the UK as a recommended treatment for patients with schizophrenia since the early 2000s. In the UK, the National Institute for Health and Clinical Excellence (NICE) recommends that cognitive behavioural therapy should be made available to all people suffering with schizophrenia, particularly those with persistent hallucinations and delusions, lack of insight, and poor concordance with antipsychotic medications (NICE, 2002). Similar recommendations have been made in Canada (Canadian Psychiatric Association, 2005) and the US (American Psychiatric Association's Practice Guideline for the Treatment of Patients with Schizophrenia, 2004 and Guideline Watch (September 2009): Practice Guideline for the Treatment of Patients with Schizophrenia; PORT schizophrenia recommendations 1998, 2004, 2010). In addition, the Netherlands and Australia have developed research programmes in this area and Brazil, China, Germany, Japan, Scandinavia and Spain are all showing an increasing research interest in this approach (Beck, in Turkington et al., 2009).

3.2 Case study scope

This case study will discuss the development of CBT for psychosis in the UK, the US and Canada. The aim of this work is not just to examine the history and development of CBT as a treatment for schizophrenia, from the initial research to its final recommendation as a treatment in the clinical guidelines for schizophrenia in the UK, the US and Canada, but also to highlight issues and events that either assisted or blocked the advance of research into this area of study and the adaption of CBT techniques and practices to the treatment and management of schizophrenia.

It should be stressed that this case study is not intended to establish the evidence base for CBT for psychosis or to make a judgement on its efficacy as a treatment for schizophrenia. Rather, we will comment on the key enablers and barriers that both facilitated and impeded the research and development of this treatment, including broader societal and cultural factors, and make observations on the factors involved in developing a potential treatment from the initial research to its adoption by medical practitioners as a treatment for schizophrenia.

3.3 Glossary

Adherence therapy

Adherence therapy is a specific cognitive behavioural approach that aims to enhance compliance with medication.

Behavioural therapy

Behavioural therapy aims to change any behaviours that are harmful or not helpful using various techniques. For example, a common unhelpful behaviour is avoiding situations that can make an individual anxious. In some people with phobias this avoidance can

[4] There is still controversy about the effectiveness of CBT versus other psychosocial treatments, and some reviews continue to highlight challenges with the CBT RCT methodologies (eg Lynch et al., (2010); Jones, Hacker, et al., 2011).

become extreme and affect day-to-day life. In these cases, a type of behavioural therapy called exposure therapy may be used whereby exposure to feared situations is gradually built up. The therapist teaches the individual how to control anxiety when faced with a feared situation by using deep breathing and other techniques.

Cognitive behavioural therapy (CBT)

CBT is a type of psychotherapy (or 'talking therapy') that is based on the theory that psychological symptoms are related to the interaction of thoughts, behaviours and emotions. The term CBT embraces a wide range of therapeutic and research approaches to helping people deal with and solve emotional, behavioural and cognitive (thinking) issues and problems such as depression, anxiety, OCD and fear-related issues. Sara Tai and Douglas Turkington define CBT as an 'evidence-based talking therapy that attempts cognitive and behavioural change based on an individualised formulation of a client's personal history, problems, and world views (Tai and Turkington, 2009). The Cochrane Review, which has discussed the difficulties of providing a single, unambiguous definition of cognitive behaviour therapy, given the variety of interventions that have been ascribed this label, describes CBT as follows:

> In cognitive behavioural therapy (CBT) links are made between the person's feelings and patterns of thinking which underpin their distress. The patient is encouraged to take an active part by: (i) examining the evidence for and against the distressing belief; (ii) challenging the habitual patterns of thinking about the belief; and (iii) using reasoning abilities and personal experience to develop rational and personally acceptable alternative explanations and interpretations (Cormac et al, 2004).

Cognitive Therapy (CT)

Cognitive therapy is a form of therapy developed in the 1960s by Aaron Beck, who suggested that our beliefs and perceptions influence our emotional responses to the world around us. According to cognitive therapy, our negative thought patterns (not unconscious conflicts or early life traumas as psychoanalysis suggests) cause depression, anxiety and some other mental disorders. Cognitive therapy helps patients by making them aware of these beliefs and how they produce so many problems, and then working to change these dysfunctional beliefs.

Family psychoeducation

Family psychoeducation is a method of working in partnership with families to impart current information about the illness and to help them develop coping skills for handling problems posed by mental illness in one member of the family. The goal is that practitioner, consumer and family work together to support recovery.

Graded activity programme

Graded activity programmes refer to treatment programmes whereby exposure to a situation or activity is gradually built up and increased from a baseline.

Intrusions

Intrusive thoughts are negative and distressing thoughts that are unwanted and feel uncontrollable to the individual experiencing them.

Negative symptoms

Negative symptoms are deficits of normal emotional responses or other thought processes, and respond less well to medication than positive symptoms (described below). They commonly include flat or blunted affect and emotion, poverty of speech, inability to experience pleasure, lack of desire to form relationships and lack of motivation. Research suggests that negative symptoms contribute more to poor quality of life, functional disability and the burden on others than positive symptoms. People with prominent negative symptoms often have a history of poor adjustment before the onset of illness, and response to medication is often limited.

Positive symptoms

Positive symptoms are those that most individuals do not normally experience but which are present in people with schizophrenia and other mental illnesses. They can include delusions, disordered thoughts and speech, and tactile, auditory, visual, olfactory and gustatory hallucinations, typically regarded as manifestations of psychosis. Hallucinations are also typically related to the content of the delusional theme. Positive symptoms generally respond well to medication.

Psychoeducation

Psychoeducation is one component of many types of psychotherapy for borderline personality disorder (BPD) and other mental health conditions. During psychoeducation, the patient is provided with knowledge about the psychological condition, the causes of that condition, and the reasons why a particular treatment might be effective for reducing their symptoms.

Rational emotive behaviour therapy

Rational emotive behaviour therapy is an early version of CBT developed in 1960s by Albert Ellis. It focuses on uncovering irrational beliefs, which may lead to unhealthy negative emotions, and replacing them with more productive rational alternatives.

Safety behaviours

Safety behaviours are also known as partial avoidance behaviours. They refer to actions taken to minimise anxiety and reduce harm within a feared situation.

Stress-vulnerability models

Stress-vulnerability models suggest that a vulnerability to psychosis is acquired through a genetic predisposition or as a result of an environmental insult to the brain (for example, head injury). This vulnerability, however, is not considered to be sufficient to manifest the disorder and must be 'triggered' by environmental processes. The environmental component can be biological (such as an infection, or even drugs and alcohol) or psychological (stressful living situation, school exams, travel, etc).

Talking therapies

Talking therapies is the generic name for a range of psychotherapies, including psychoanalysis, cognitive behavioural therapy and counselling or counselling psychology approaches.

3.4 Narrative

The development of antipsychotic medication in the early 1950s led to a major transformation in the treatment of patients with schizophrenia. Previously, institutionalisation had been the standard response, and though the government had already begun to shut down these facilities, development of chlorpromazine and other antipsychotic medications greatly accelerated the move away from institutionalised care.[5] At this time, biological thinking about schizophrenia and psychoses was the dominant model in research, and biological treatments remained the established management approach for the next 30 years. A key outcome of this mainly pharmacological treatment culture was that practitioners limited their verbal interactions with patients to diagnosing their condition and prescribing a suitable medication (Haddock and Slade, 1996). Some of the earliest attempts at a psychological approach to the treatment of schizophrenia were Freida Fromm-Reichmann's 1950 work on psychotherapy for psychotic patients (Fromm-Reichmann, 1950) and H. S. Sullivan's 1947 *Conceptions of Modern Psychiatry*, which included a modification of psychoanalysis designed to enhance better integration into a hospital environment (Sullivan and Mullahy, 1947). These pioneering efforts increased awareness of the psychological processes and personal impact of schizophrenia (NICE, 2010).

Although there was little interest in schizophrenia from the cognitive and behaviour therapy community, an early case study by A. T. Beck appeared, in 1952, which successfully applied CBT techniques in the treatment of a schizophrenic patient. Significantly, despite this study's promising results, no further work on CBT for schizophrenia was carried out for over twenty years. Beck himself abandoned any further research in this area. Following his return from the Korean War, he took up a post at the University of Pennsylvania and his focus on CBT shifted away from schizophrenia to anxiety, depression and post-traumatic stress disorder. The cessation of work on CBT for schizophrenia also coincided more widely with the introduction of antipsychotic medication and with it the growing belief that drug treatment would be the most successful means of managing schizophrenia.

Throughout the 1970s, the move from institutionalised treatment gathered pace. Psychological and social research into factors that might contribute to relapse in people living in community settings – such as stressful life events and communication difficulties in families (high expressed emotion) – stimulated the development of family interventions to prevent relapse (Leff et al., 1982). These family interventions, which often included education for family members about schizophrenia, developed into what is now known as 'psychoeducation' or 'family psychoeducation' (NICE, 2010, 28).

[5] Other factors contributed to deinstitutionalisation, such as growing concerns about the abusive conditions found in many state psychiatric facilities which were considered to be at least as harmful as the mental illness itself, economic considerations in light of the expense of housing mentally ill patients in these facilities, and, in the US, the Civil Rights movement led many to believe that the civil rights of the mentally ill were being violated. The discovery of chlorpromazine made it possible to effectively manage the treatment of patients outside of a hospital setting, and deinstitutionalisation began in the UK and Norway from early 1950s. However, it should be noted that in Japan and elsewhere in the Far East, the availability of chlorpromazine did not have the same impact on hospitalisation rates and the institutionalisation of patients continued up to the 1970s and 1980s.

From the late 1970s onwards, the theoretical understanding of schizophrenia was changing, as stress-vulnerability models that incorporated psychological and social elements were being developed and empirically tested (eg Zubin and Spring, 1977; Nuechterlein and Dawson, 1984). This theoretical interest in the psychotic process itself, and the more optimistic attitude that psychosocial treatments could have a significant benefit in the days of de-institutionalisation and community care, set the scene for the development of CBT approaches to reduce the symptoms of schizophrenia.

As CBT was originally developed for the treatment of patients with non-psychotic disorders such as depression or anxiety, it was this treatment model that informed the development of specialised CBT treatments for psychoses. The research that was being carried out into intrusions and safety behaviour in anxiety disorder was transferred into theoretical models of psychosis (eg Morrison, 2001; Morrison et al., 1995) and broader cognitive models of schizophrenia were subsequently developed (Garety, 2001).

Early forms of CBT for schizophrenia focused on improving coping (Tarrier, 1992), building social and independent living skills, and increasing compliance with treatment using behavioural strategies such as linking taking tablets to another activity (Weiden, 1995). Negative symptoms were targeted by providing graded activity programmes (Meichenbaum and Cameron, 1973). These approaches have continued to be applied where deficit symptoms of schizophrenia and improving functional outcomes are the main focus of intervention (Hogarty et al., 1991).

Despite these developments, the move towards applying CBT techniques to the treatment of schizophrenia was slow, through the 1970s and 1980s, as a number of prejudices about the nature of the illness and its amenability to cognitive or behavioural therapeutic approaches remained rooted in the research and clinical community. In 1986, A. S. Bellack, in his Presidential address for the Association for Advancement of Behavior Therapy (AABT), termed schizophrenia 'the forgotten child of behaviour therapy' (Bellack, 1986 [qtd. in Tarrier and Wykes, 2004]), alluding to the dominant focus on anxiety and depression in the literature about CBT. Bellack argued that schizophrenia had been ignored by behaviour therapists because of four mistaken assumptions: '(a) the belief that the diagnosis is an over-generalised label and the disorder does not exist, (b) the belief that the disorder has a biological basis and, thus, is not in the purview of behaviour therapy, (c) the belief that schizophrenia is adequately treated by medication, making behaviour therapy superfluous, and (d) the belief that it is too severe for behaviour therapy' (Bellack, 1986). The gradual erosion of these prejudices from the 1980s onwards became crucial to the subsequent development of CBT techniques to treat schizophrenia.

By the late 1980s, the use of CBT had expanded enormously and the possibility of its application to other areas was increasingly considered. Building on successful treatment studies in affective disorder, CBT was becoming the established treatment of choice for many non-psychotic conditions. According to Tarrier and Wykes, '[i]t was inevitable that CBT would be tried as a possible treatment for schizophrenia.' (Tarrier and Wykes, 2004). There was a growing recognition that cognitive theory and interventions for anxiety, social phobia, PTSD and obsessive-compulsive disorder (OCD) could also find application within the practice of CBT for psychosis (Tai and Turkington, 2009). An example of this

is the work of Chadwick et al. (Chadwick et al., 1996) which, leading on from Beck's work on OCD, demonstrated that voices could be conceptualised as intrusive thoughts.

A number of single case studies emerged from the UK in the late 1970s and throughout the 1980s (Watts et al., 1973; Milton et al., 1977; Hole, et al., 1979; Alford, et al., 1982; Hartman and Cashman, 1983). On the basis of this early evidence, randomised controlled trials began to take place in earnest from the early 1990s onwards. It was from this point that the evidence for the efficacy of CBT for schizophrenia began to accumulate and, with the publication of the RCT results, the subject received greater attention from the wider research and clinical community, both in the UK and overseas.

The evidence base for the efficacy of CBT has primarily come from randomised trials in the UK. Throughout the 1990s a small number of UK-based researchers, including Richard Bentall, David Fowler, Philippa Garety, Gill Haddock, David Kingdon, Elizabeth Kuipers, and Douglas Turkington, championed the development of cognitive behavioural interventions for psychotic patients, either as direct therapies for specific symptoms (eg Bentall et al., 1994; Chadwick and Birchwood, 1994; Chadwick and Lowe, 1990; Fowler and Morley, 1989; Garety et al., 1994; Haddock et al., 1993); as a way of enhancing patients' coping skills (eg Tarrier et al., 1990; Tarrier et al., 1993); or as part of a normalising strategy designed to make patients more accepting of what would otherwise be disturbing experiences (eg Kingdon et al., 1991; Kingdon et al., 1994). In fact, the sustained commitment of these researchers to devote research to developing a cognitive model of schizophrenia – particularly in the context a predominantly biological approach to schizophrenia and a widely-held prejudice about the value of 'talking therapies' for psychoses – emerges as a key factor in the evolution of CBT techniques for schizophrenia and a major contributor to the evidence base that current treatment approaches to schizophrenia have been drawn upon.

A number of studies, (eg Kingdon and Turkington, 1994; Fowler et al., 1995) described how CBT for disorders such as anxiety and depression could be adapted for and applied to the treatment of schizophrenia. There are a number of ways in which CBT was amended for schizophrenia. The problem of stigma, for example, was addressed by identifying the negative assumptions that people held about schizophrenia and then providing evidence that some of these experiences are common in the general population: a process known as 'normalising' (Tai and Turkington, 2009). By providing alternative explanations for the symptoms of schizophrenia, patients were able to adopt a more positive outlook on their condition and potential for recovery (Harrison et al., 2001). CBT for schizophrenia also involved shorter sessions than CBT for other disorders, with more flexible sessions and simplified homework (Tai and Turkington, 2009). In addition, the role of sleep disturbance, affect, and safety behaviours (for example, behaviours such as avoidance that maintained faulty beliefs) was identified to produce 'mini-formulations' of positive symptom maintenance (Morrison et al., 1998).

In the midst of this mounting body of research, two key conferences took place in the early 1990s, in Liverpool and Vancouver, which were crucial in galvanising the growing interest in cognitive or psychological approaches to psychosis. A specific cognitive behavioural approach that aims to enhance compliance with medication was also developed towards the mid 1990s. In the UK, this approach is now commonly known as 'adherence therapy'

(Kemp et al., 1996; NICE, 2010, 28). In the US, CBT strategies aimed at improving medication adherence and helping patients manage their illness form the backbone of 'illness management and recovery', a multi-component intervention 'designed to help individuals with serious mental illness collaborate with professionals, reduce their susceptibility to the illness, and cope effectively with their symptoms.' (Mueser et al., 2004).

The multidisciplinary nature of scientific research in the UK has been a key reason that CBT was developed as a treatment for schizophrenia here first. In the US, the separation of the practice of psychology and psychiatry naturally precluded the crossover and collaboration that was so readily available in the UK and which made the adaption of psychosocial techniques to mental illness so much easier in the UK. Similarly, funding for this kind of work was more available, and remains more available, in the UK than the US, where funders favour medical treatment of schizophrenia.

Meetings between researchers working on psychological treatments for schizophrenia also were first held in the 1990s, by invitation only: the first International Conference on Psychological Treatments for Schizophrenia was held in Cambridge, UK in 1995 and annual meetings between UK and North America-based researchers were held, at the instigation of A. T. Beck, from 1998 onwards. In fact, these largely informal meetings have been critical in advancing the development and use of CBT for schizophrenia by allowing researchers to share current hypotheses and emerging research findings, and discuss each other's work.

It was not until the early 2000s that the first trials of CBT for psychosis to be funded by the Canadian Institutes of Health Research (CIHR) were started (Lecomte et al., 2008). As US research and journals are more readily available to Canadian researchers than UK research and journals, it was not until after interest in the subject of CBT for schizophrenia had taken off in the US, albeit on a small scale, that it managed to make an impact in Canada. Canadian researchers, such as Tania Lecomte, who had carried out studies in US institutes or had collaborated with US colleagues, became interested in this growing area of research and pursued funding in Canada to carry out Canada-specific research on the subject. Again, the Beck meetings, to which some key Canadian researchers were invited, were very significant in promoting this area of research in Canada and once work started being carried out in this area, Canadian research started to develop at a faster pace than in the US, where research was still more focused on social skills training and antipsychotic drug treatment. An early obstacle to the development of CBT as a treatment for schizophrenia in Canada, however, was the fact that, traditionally, psychologists in Canada do not work directly with mentally ill patients in the public sector; they more commonly practise in the private sector. As a consequence, there was not the capacity to practise CBT on an individual basis with schizophrenic patients. As a result, the focus in Canada leaned towards group therapy and developing CBT treatments for schizophrenic patients within a group setting.

Adoption and evolution of CBT in national guidelines

In the UK, the National Institute for Clinical Excellence (NICE) first recommended that CBT be offered to individuals with residual symptoms of schizophrenia in 2002 (NICE, 2002). In fact, the NICE guideline had a considerable international impact and the

endorsement of CBT as a treatment for schizophrenia was more emphatic than even the researchers who had provided the evidence base had expected. Although there had previously been guidelines in the UK, issued from the Royal College of Psychiatrists, the British Psychological Association and the Government, which were all supportive of CBT for psychosis, the NICE guideline represented a major endorsement of this treatment. The NHS then adopted CBT as a treatment for schizophrenia in 2003. In 2009, the updated NICE guidelines stated that CBT should be routinely used in the treatment of schizophrenia. According to the Cochrane Review (Jones, Hacker et al., 2011), CBT has yet to become as widely available for people with schizophrenia as it is for people with other disorders, such as depression.

While NICE recommended CBT as a treatment for schizophrenia as early as 2002, its American counterpart, the American Psychiatric Association was slower to make its own endorsement, initially characterising CBT as a supportive technique that 'may benefit' patients (Lehman et al., 2004). However, following the Schizophrenia Patient Outcomes Research Team's (PORT) recommendation of CBT as a standard of care for individuals with schizophrenia in the US, the American Psychiatric Association (APA) made a similar recommendation in its 2004 practice guidelines. In the US, the first set of PORT recommendations, published in 1998, mentioned 'behavioral and cognitive skills training approaches' among other psychological treatments with suggestive yet limited empirical evidence of benefit when 'added to pharmacotherapy for persons with schizophrenia' (PORT, 1998). For the 2004 update, however, PORT researchers cited many more methodologically sound studies; on a scale 1–3 where 1 is best, they rated the level of evidence as 1.67 (SD 0.59) (PORT, 2004). In a more recent update (2010), CBT continues to be profiled as a recommended psychosocial treatment with a strong evidence base (PORT, 2010).

The 2005 Canadian Psychiatric Association (CPA) clinical practice guidelines also endorse the use of CBT as a treatment for schizophrenia, advising that '[c]ognitive therapy should be offered to treatment-resistant patients.' (CPA, 2005, 35S). The guidelines further state that '[c]ognitive-behavioural interventions should be considered in the treatment of stress, anxiety and depression in patients with schizophrenia' (CPA, 2005, 36S). The lack of psychologists working in the public sector, however, remains a barrier to the wider practice and availability of CBT as a treatment for schizophrenia. Although there is wide support for CBT for psychosis, the lack of practitioners within a public setting has limited its use as a treatment. More usually, patients must seek private therapy or, rarely, receive CBT as part of a research study.

A recent survey of clinical practice of CBT for schizophrenia in the UK and the US revealed that UK participants were more likely to practise CBT, rated the effectiveness of CBT more highly and estimated the chances of recovery from schizophrenia more highly. US participants rated the effectiveness of medication more highly and were more likely to report the use of medication as a treatment modality (Kuller et al., 2010). These findings suggest that when it comes to CBT for psychosis, fundamental differences in the practices and attitudes of US and UK clinicians remain. Despite the endorsement of CBT for psychosis in US national clinical guidelines, this survey suggests that US clinicians are still less likely to practise CBT than their UK counterparts. The reasons for this disparity may be linked to differences in the structure and organisation of national healthcare delivery

systems, clinical research funding priorities, and attitudes towards schizophrenia and the nature of mental illness itself.

3.5 Observations - barriers

Biological/medical disease view of schizophrenia meant that clinicians and researchers were not open to the possibility that cognitive therapy could alleviate symptoms or help manage the condition.

For many years a biological explanation of schizophrenia dominated thinking on the illness. This meant that schizophrenia was viewed primarily as a biological condition and that its symptoms were related to changes in brain activity and its physiology. Those who subscribed to this interpretation of schizophrenia believed, as a consequence, that only antipsychotic medication could control and alleviate the symptoms associated with the illness. A large proportion of the literature on schizophrenia has been in support of this medical disease model of schizophrenia For example, studies of families, twins, adoptive children and so forth (Gottesman and Shields, 1996; Sherman et al., 1997) have argued that schizophrenia is a condition with a strong genetic predisposition, while studies on the functioning of the dopamine neurotransmitter in schizophrenia have implicated biochemical problems in the brain in the development of schizophrenia. This led to a firm prejudice that a 'talking treatment' could not possibly produce positive outcomes in a brain disease, a view that was particularly prevalent in the US and one that Beck discussed in his foreword to Kingdon and Turkington's Cognitive-Behavioural Therapy of Schizophrenia (Kingdon and Turkington, 1994). In the UK, however, there was a very strong tradition of rehabilitation and a group of psychologists who were working with rehabilitation approaches began using an understanding of cognitive processes to inform these approaches, particularly in centres at Manchester, Birmingham and London. From the mid- to late-1980s onwards, cognitive research began to identify cognitive processes that were associated with psychosis and which lent themselves to more specific interventions than the broad rehabilitation approaches that had previously been used. This coincided with the emergence of a growing literature on CBT for depression and anxiety. With a greater appreciation of the role that environmental and psychosocial factors play in the development of the disease, a new model of schizophrenia began to emerge that laid the foundations for the development of cognitive behavioural therapies for psychosis. Central to this change in thinking was Beck's 1979 work (Beck et al., 1979) on cognitive therapy for depression, which recognised the significance of learnt behaviours and conscious thinking and facilitated the development of cognitive models of schizophrenia.

Evidence base has been characterised by gaps and inconsistent findings

Despite clear indications that CBT has a beneficial effect on psychotic symptoms, questions remain, (Tai and Turkington, 2009) including why it is that CBT works for some patients and not for others. A key objection made by those who question the efficacy of CBT for schizophrenia is that one of the most widely quoted trials in support of its efficacy (Kuipers et al., 1997) employed neither a control intervention nor blind evaluations (Turkington and McKenna, 2003). Most recently, a 2010 article in *Psychological Medicine* (Lynch et al., 2010) stated that no trial employing both blinding and psychological placebo has found CBT to be effective in either reducing symptoms or preventing relapse in schizophrenia. Similarly, despite claims (Sensky et al., 2000) that the

use of CBT leads to sustained clinical improvement in schizophrenia, the 2004 Cochrane review (Jones et al., 2004) found no convincing evidence of its effects in the longer term. However, more recently, a two year follow-up study by Malik et al and a five year follow-up to the Sensky et al. project did show evidence of enduring effects (Malik et al., 2009; Turkington et al., 2008). Researchers from the Schizophrenia Patient Outcomes Research Team (PORT) recently summarised the problem areas in the evidence base for CBT. These are inconsistent findings regarding its effects on residual psychotic phenomena, and a paucity of evidence regarding its effects on depression, suicidal tendencies, relapse, recent onset schizophrenia and acute psychotic exacerbation in chronically ill patients.

Another important issue is the degree to which CBT may be feasibly implemented in routine practice and delivered with fidelity (integrity). This is a particular issue in the US where workforce limitations and issues related to the financing and organisation of the specialty mental health system have limited the adoption of psychosocial interventions and tipped the balance in favour of medication-based treatment (Frank et al., 2004; Hadjipavlou et al., 2009; Olfson et al., 2009). Implementation considerations rather than intrinsic patient-differences justify the call for US-specific research on the effectiveness of CBT for schizophrenia.

3.6 Observations - enablers

De-institutionalisation paved the way for treatment of schizophrenic patients in the community

The movement away from institutional or hospitalised treatment of mentally ill patients laid the pathway, not only for the development and wider use of antipsychotic drugs, but also for psychosocial treatments, including CBT, that patients could receive within a community setting.

Two conferences, held in 1990 and 1991, were critical to the development of CBT for psychosis.

Two seminal conferences on CBT for psychosis were held in 1990 and 1991 place which advanced interest in this area of study and enabled the sharing of research and approaches to the CBT for psychosis between researchers and research institutes.

15–18 July 1990: a conference held in Vancouver, entitled 'Schizophrenia: Poised for Discovery'. This was a seminal schizophrenia conference organised by the local mental health service in the university. Initially intended as a small meeting on developments in psychological treatments for psychosis, the event attracted a large crowd, demonstrating the growing interest in this subject. Attending this event were leading UK researchers in this area such as Douglas Turkington, David Kingdon, Paul Bebbington and Elizabeth Kuipers and the meeting provided an early opportunity for the representatives of these different research groups to share their research findings and create opportunities for future collaboration.

June 1991: a one-day conference, set up by Gill Haddock and Richard Bentall, held at the University of Liverpool. Haddock and Bentall invited researchers from UK,

including Philippa Garety and David Fowler, who were becoming interested in CBT for psychosis. This conference played a key event in crystallising the emerging interest in this subject. The gathering confirmed the interest of mental health researchers and professionals in exploring the possible value of these methods as an adjunct or alternative to traditional psychopharmacological approaches in the management of psychosis.

An informal workshop organised by A. T. Beck in 1998 evolved into a series of annual meetings of UK and US researchers working on CBT for Schizophrenia. Important studies and collaborations have arisen out of these meetings.

Beck invited Kingdon and Fowler to do a workshop at the Beck Institute. Other key researchers, including UK-based Phillipa Garety and David Fowler and US-based Glen Gabbard, also took part. This was the first time that these disparate researchers, who were all interested in CBT for schizophrenia and were developing research in this area, came together to discuss current research and approaches. The following year, a similar meeting was held in Southampton in the UK. This led to a series of annual meetings, alternating between North America and Europe whereby researchers interested in this area of study gather to discuss new research ideas and new results for the efficacy of CBT for schizophrenia. Significantly, these meetings have been funded primarily by the participants themselves and their success has been attributed to the individual commitment of the researchers themselves, with Beck as the original instigator, to come together to share their ideas and advance research in the area of CBT for psychosis. A number of research partnerships have originated at these meetings.

Shift in attitudes towards schizophrenia, from biological understanding of the disease to a psychosocial one, precipitated new focus on possibility of adapting CBT for Schizophrenia

The deeply held prejudice that schizophrenia was a primarily biological condition and could only be effectively treated with medication took several decades to be overcome. As the use of CBT expanded throughout the 1980s, the possibility of adapting the therapy to the treatment of schizophrenia was increasingly considered. A psychosocial, or cognitive, explanation of schizophrenia acknowledges the role of biological factors as the cause of the initial sensory experience of schizophrenia, but places greater importance on how the individual interprets the features of the disorder, believing that some of the more distressing aspects can be alleviated if the patient can change how they interpret, understand, and respond to the symptoms of the illness.

Independent agency of some researchers throughout the 1990s was crucial in advancing research into CBT for schizophrenia and in developing outside interest in the subject.

The evidence base for CBT for schizophrenia that has emerged in the UK is remarkable for the prominence of a small coterie of researchers who have been associated with the research and who have actively championed the study of this field. It is difficult to overstate the impact that these researchers, including Richard Bentall, David Fowler, Philippa Garety, Gill Haddock, David Kingdon, Elizabeth Kuipers, and Douglas Turkington, have had on the development of CBT for psychosis, not just in the UK but subsequently across the

world. It was their individual interest and belief in the potential for adapting cognitive theory to the treatment of schizophrenia that led these researchers to pursue funding for research into this area of work and to carry out trials into the efficacy of CBT for schizophrenia. In the same way, the personal effort by Beck to gather researchers on CBT for schizophrenia together in an informal setting to discussion current research and future study has proven critical to the development of the evidence base and the promotion of the field of study across the US and Canada. Crucially, these meetings took place without sponsorship or external funding and were organised and funded – and continue to be organised and funded – solely by the researchers concerned. From the late 1990s onwards, these researchers also started participating regularly in the American Psychiatric Association annual conferences, running workshops on CBT for psychosis and/or participating in pre-conference workshops. This activity has resulted in collaborative works between US-based and UK-based researchers (eg Wright et al., 2009). Without these researchers' independent dedication to the development and promotion of the CBT as a treatment for schizophrenia, it is very likely that the treatment would not have developed at the pace it did nor reached the level of application that it has achieved across the world.

3.7 Other observations

National healthcare delivery models have influenced how CBT for schizophrenia has been used clinically in UK and US.

In the UK, the NHS has contributed to the multidisciplinary approach to healthcare and research that has enabled the UK to develop cognitive therapy for schizophrenia so effectively and so successfully compared with other nations that do not have a similar healthcare delivery model. In the US, the separation of the practice of psychology and psychiatry has prevented the same level of collaboration/multidisciplinary approach to treatments for schizophrenia and other illnesses.

In addition, research funding in the US is more widely available in biological psychiatry and this has contributed to the prominence of biological psychiatrists in medical schools who continue to favour this approach to the treatment of schizophrenia. The American Psychiatric Association commissioned a study that suggested that reasonable psychiatrists will not practise psychotherapy as they will not make more than $100,000 a year, whereas three times that amount can be made by evaluating and medicating (Karon, 1995).

1907

1907 Carl Jung was one of the first clinicians to advocate for individual psychotherapy for people with schizophrenia (Switzerland). [Other Nation]

1950

De-institutionalisation paves way the for treatment of schizophrenic patients in the community.

Discovery of Chlorpromazine leads to pharmacological revolution in the treatment of schizophrenia. It is now possible to treat schizophrenia patients with antipsychotic drugs. Pharmacological treatment of schizophrenia is dominant from this point onwards.

1950 Frieda Fromm-Reichmann publishes Principles of Intensive Psychotherapy, in which she explains her neo-Freudian theory and therapy for treating psychotic patients. (Germany) [Other Nation]

1957 Freud maintained that psychoanalysis would not work with schizophrenics because such patients ignore their therapist's insights and are resistant to treatment (Dolnick 1998: 40).[-VE]

1952 Early paper by A.T Beck applies CBT techniques in the treatment of a schizophrenic patient. [USA]

1960

1970

1962 Albert Ellis publishes Reason and Emotion in Psychotherapy, a milestone in the development of rational-emotive therapy (RET). (Ellis, A. (1962) Reason and Emotion in Psychotherapy. Lyle Stewart, New York)[USA]

1973 Watts, et al. The modification of abnormal beliefs. Behaviour Journal Medicine and Psychology, 46, 359-363. This study involved three male subjects, with an average of 9.3 years with the disorder. Participants had low to moderate SZ. Findings suggest CBT has the potential to be effective in conviction and general complaints.

1976 CBT developed for treatment of depression (Beck, A.T. (1976) Cognitive Therapy of Depression, Guilford Press, NY.1976) [USA]

1977. Milton, F., Patwa, V. K., & Hafner, R. J. (1977). Confrontation vs. belief modification in persistently deluded patients. British Journal of Medical Psychology, 51, 127-130. It is concluded verbal intervention of an appropriate kind can substantially reduce the overall psychiatric disturbance of a proportion of persistently deluded patients.

1979 AT Beck collaborates on a study with Richard Hole and John Rush (Hole, Rush, & Beck, 1979) in which cognitive interventions were applied in a more systematic way with the delusions of several patients who had schizophrenia – with promising results. [USA]

1980

1982 Alford, G. S., Fleece, L., & Rothblum, E. (1982). Hallucinatory-delusional verbalizations: Modification in a chronic schizophrenic by self-control and cognitive restructuring. Behavior Modification, 6, 421-435

1983. Hartman, L. M., & Cashman, E E. (1983). Cognitive-behavioral and psychopharmacological treatment of delusional symptoms: A preliminary report. Behavioural Psychotherapy, H, 50-61.

1985 Throughout the 1980s, consistent findings that family environments, in terms of the measure of expressed emotion (EE) (Leff & Vaughn, 1985) were strongly influential in determining the recurrence of schizophrenic symptoms promoted the development of family interventions that were successful in reducing relapse (Pilling et al, 2002; Tarrier & Bobes, 2000). [UK]

1985 Main proponents of CBT work started drawing on cognitive psychology and CBT as it was applied to psychosis and testing these approaches.[+VE]

1985 Strong tradition of rehabilitation in UK meant that a group of psychologists who were working using rehabilitation approaches were also taking cognitive approaches and using cognitive understanding in their rehabilitation. This was in a number of centres in the UK, principally Manchester, Birmingham and London.[+VE]

1986 Association for the Advancement of Behavioural Theapy (AABT) Presidential address by A.S. Bellack describes schizophrenia as 'behaviour therapy's forgotten child' and questions the erroneous assumptions about schizophrenia that prevented behaviour therapists from working on the disorder. [USA]

In the US, the separatio of psychology and psychiatry has prevented the same level of collaboration/multidisciplinary approach to treatment that has prevailed in the UK and which has facilitated the development of cognitive therapy for illnesses such as schizophrenia.

1988 Tyrer, P., et al. The Nottingham Study of Neurotic Disorder Comparison of Drug and Psychological Treatments. The Lancet 332:8605 (1988) 235-240. [UK]. 210 psychatric outpatients with generalised anxiety disorder, or panic disorder were allocated to one of five treatments: diazepam, dothiepin, placebo, cognitive and behavior therapy and a self-help treatment therapy. It was found that diazepam was less effective than dothiepin, cognitive and behaviour therapy, or self-help. More patients in the placebo group took additional psychotropic drugs in the trial period, and those allocated to dothiepin and cognitive and behaviour therapy took the least.

1988 David Kingdon was working on the Nottingham Neurosis Study (Tyrer et al, 1988, 1990) in which cognitive therapy was employed by a group of patients with neurotic disorders. Kingdon realised that the techniques he was using with patients who had psychoses could be described as a variant of cognitive therapy. This prompted him and colleagues to define the techniques used, incorporate additional components and refine them.

Research funding in the US is more widely available in biological psychiatry and this has contributed to the prominence of biological psychiatrists in medical schools who continue to favour this approach to the treatment of schizophrenia.

1990

1990 Development of cognitive-behavioural interventions for psychotic patients as direct therapies for specific symptoms (Chadwick and Lowe, 1990) and as a way of enhancing patients' coping skills (e.g. Tarrier et al., 1990) [UK]

1990 Vancouver conference. Seminal schizophrenia conference organised by the local mental health service in the university. Initially intended as a small meeting on developments in psychological treatments for psychosis, the event attracted a large crowd, demonstrating the growing interest in this subject. Attending this event were leading UK researchers in this area such as Douglas Turkington, David Kingdon, Paul Bebbington and Elizabeth Kuipers

1990 Psychotherapy, in the form of psychodynamic psychotherapy was largely discredited as a treatment for schizophrenia (Mueser & Berenbaum, 1990) [USA]

1991. Study by the Newcastle Group: Development of cognitive-behaviour processes for psychotic patients as part of a normalising strategy designed to make patients more accepting of distressing experiences (e.g. Kingdon and Turkington, 1991). [UK]

1991 One day conference held at University of Liverpool on 'Psychological Approaches to the Management of Psychosis.' [UK]

1992 and 1993: studies on individual CBT by the Manchester Group: Tarrier N. Psychological treatment of schizophrenic symptoms. In: Kavanagh D, ed. Schizophrenia: An Overview and Practical Handbook. London, UK: Chapman & Hall; 1992. This early form of CBT for schizophrenia focused on improving coping. [UK]

1992 Chris Frith publishes The Cognitive Neuropsychology of Schizophrenia which introduces the idea that some symptoms of schizophrenia, such as thought-insertion and verbal auditory hallucinations, represent failures to self-monitor one's own thinking or conscious mental activity. [UK]

1995

1994 Small scale studies by research groups at London-East Anglia, Liverpool and Birmingham. Further development of cognitive-behavioural interventions for psychotic patients as direct therapies for specific symptoms (e.g. Bentall et al., 1994; Chadwick and Birchwood, 1994; Garety et al., 1994) [UK]

1995 First International Conference on Psychological Treatments for Schizophrenia. 28-29 September 1995, Robinson College, Cambridge, England. This is a biannual event. [UK]

1995 Fowler D, Garety P, Kuipers E. Cognitive-Behaviour Therapy for psychosis: Theory and Practice. Chichester, UK: Wiley;1995. [UK]

1996 Birmingham Group: Randomised controlled trial of cognitive behaviour therapy with acute inpatients (Drury et al, 1996; Kemp et al, 1996). [UK]

1996 By this time there was enough evidence from the single case studies of the late 1980s and early 1990s to start generating RCTs. These RCTs built up considerably throughout the mid-1990s. [+VE]

1997 London East Anglia Group: Randomised controlled trial of CBT with 60 patients with mediation-resistant pyschosis (Kuipers et al, 1997). [UK]

2000

1998 Beck had begun to hear about the RCTs in the UK and starting the reading the literature. He invited the researchers to the US in order to find out more about what the therapy involved and how compatible it was his understanding of cognitive therapy. This was a significant meeting because it was the first time that UK researchers had formally met together. It also meant that Beck became a prominent 'champion' of CBT for schizophrenia is the US. At the instigation of Beck, this is now an annual meeting which is held either in Europe or North America to discuss progress. [+VE]

1998. Manchester Group: RCT by Tarrier et al (1998) provides further important empirical evidence on the specificity of CBT above nonspecific benefits of supportive psychotherapy (Tarrier et al, 1998). [UK]

2000 Randomised controlled trial of CBT with people with mediation-resistant pyschosis (Sensky et al, 2000)

2002 Randomised controlled trial of CBT as a treatment for schizophrenia (Turkington et al, 2002) [UK]

2002 'Schizophrenia: Core Interventions in the Treatment and Management of Schizophrenia in Primary and Secondary Care' was the first National Institute of Clinical Effectiveness (NICE) guidance to be produced in 2002. This guidance includes a recommendation that CBT (and family interventions) be used in the treatment of schizophrenia. [UK]

2003 NHS adopted cognitive therapy as a valid treatment for schizophrenia. [UK]

2004 New studies support for role of CBT in reducing both positive and negative symptoms of schizophrenia (Trower et al, 2004) and improving social functioning (Startup M, Jackson MC, Bendix S, 2004). [UK]

2000 Randomised controlled trial of cognitive therapy and recovery from acute psychosis (Drury et al, 2000) [UK]

2004 American Psychiatric Association Practice guidelines for the treatment of patients with schizophrenia includes 'cognitive behaviourally oriented psychotherapy' among the recommended treatments for patients. [USA]

2005 Canadian Psychiatric Association publishes practical guidelines recommending CBT be offered to treatment-resistant patients

2006 National Forum for Assertive Outreach. Respondents reported a lack of organisational investment, the structured nature of CBT, caseload issues, medication issues, application to people with sensory impairment, staff apathy and staff burnout as some of the barriers to the implementation of CBT for psychosis.[-VE]

2006 National Forum for Assertive Outreach Annual Conference surveyed attendees to find out what the barriers were to the implementation of psychosocial interventions in their area. [UK]

2008 Further support for role of CBT in reducing both positive and negative symptoms of schizophrenia (Turkingdon D, Kingdon D, Weiden PJ, et al, 2006; 2008). [UK]

2009 Updated NICE guidelines on schizophrenia published, advising that CBT should be offered to 'all people with schizophrenia'. [UK]

2009 Guideline Watch (September 200(): Practice Guideline for the Treatment of Patients with Schizophrenia published by the American Psychiatric Association. States that 'while recent studies continue to offer support for the role of CBT in reducing both positive and negative symptoms...', there is not consistent evidence that CBT improves outcomes among individuals who are experiencing acute psychotic symptoms. [USA]

UK

Canada

US

International

Publication or research study

Movement or cultural/attitude shift

Conference/event

3.8 References

Alford, G. S., Fleece, L., and Rothblum, E. (1982). 'Hallucinatory-delusional Verbalizations: modification in a chronic schizophrenic by self-control and cognitive restructuring.' *Behavior Modification,* 6, 421–435.

Beck, A. T., Rush, A.J., Shaw, B.F., Emery G. (1979). *Cognitive Therapy of Depression*. New York, NY: Guilford Press.

Beck, A. T., 'Forward' in Douglas Turkington, et al., (2009). *Back to Life, Back to Normality*. Cambridge, UK: Cambridge University Press.

Bellack, A. S. (1986). 'Schizophrenia: Behaviour Therapy's Forgotten Child'. *Behavior Therapy.* 17(3), 199–214.

Bentall, R. P., Kinderman, P. and Kaney, S. (1994). 'The Self, Attributional Processes and Abnormal Beliefs: towards a model of persecutory delusions.' *Behaviour Research and Therapy,* 32, 331–341.

CIHR (Canadian Institutes of Health Research) Treating psychotic symptoms of young individuals presenting a first episode of schizophrenia: comparing two state-of-the-art interventions.' Canadian Institutes of Health Research. 2001-2004.

Canadian Psychiatric Association, (2005). 'Clinical practice guidelines: treatment of schizophrenia', *Canadian Journal of Psychiatry*, 50(1).

Chadwick, P. D. and Lowe, C. F. (1990) 'Measurement and Modification of Delusional Beliefs.' *Journal of Consulting and Clinical Psychology*, 58, 225–232.

Chadwick, P. D. and Birchwood, M. J., (1994) 'The Omnipotence of Voices: a cognitive approach to hallucinations.' *British Journal of Psychiatry,* 164, 190–201.

Chadwick, P.D., Birchwood, M.J. and Trower, P., (1996). *Cognitive Therapy for Delusions, Voices and Paranoia*. Chichester, UK: Wiley.

Conley R. R. and Kelly, D.L. (2001). 'Management of treatment resistance in schizophrenia.' *Biological Psychiatry*, 50(11), 898–911.

Fowler D. and Morley, S., (1989). 'The Cognitive Behavioural Treatment of Hallucinations and Delusions: a preliminary study.' *Behavioural Psychotherapy,* 17, 267–282.

Fowler, D., Garety, P. and Kuipers, E. (1995). *Cognitive-Behaviour Therapy for Psychosis: theory and practice*. Chicester, UK: Wiley.

Frank, R. G., Berndt, E. R. et al., (2004). 'Quality-Constant "Prices" for the Ongoing Treatment of Schizophrenia: an exploratory study.' *The Quarterly Review of Economics and Finance*, 44(3), 390–440.

Fromm-Reichmann, F, (1950). *Principles of Intensive Psychotherapy*. Chicago, Illinois: University of Chicago Press.

Garety, P. A., Kuipers, L., Fowler., D., Chamberlain F., and Dunn, G. (1994). 'Cognitive Behavioural Therapy for Drug-resistant Psychosis.' *British Journal of Medical Psychology,* 67, 259–271.

Garety, P. A., Kuipers, E., Fowler, D., Freeman, D., and Bebbington, P. E. (2001). 'A Cognitive Model of the Positive Symptoms of Psychosis.' *Psychological Medicine*, (31), 189–195.

Gottesman, I. I., and Shields, J., (1966). 'Schizophrenia in twins: 16 years' consecutive admissions to a psychiatric clinic.' *British Journal of Psychiatry,* 112, 809–818.

Haddock, G., Zanna M. P., and Esses, V. M. (1993). 'Assessing the Structure of Prejudicial Attitudes: the case of attitudes towards homosexuals.' *Journal of Personality and Social Psychology,* 65, 1105–1118.

Haddock, G. and Slade, P. D. eds., (1996). *Cognitive-Behavioural Interventions with Psychotic Disorders*. London and New York: Routledge.

Hadjipavlou, G., Ogrodniczuk, J. S., et al., (2009). 'Psychiatry Without Psychotherapy?' *Archives of General Psychiatry*, 66(4), 452–453.

Harvey, A., Watkins, E. R., Mansell, W. and Shafran, R. (2004). *Cognitive Behavioural Processes Across Psychological Disorders: a transdiagnostic approach to research and treatment*, Oxford, UK: Oxford University Press.

Hartman, L. M., and Cashman, E. E. (1983). 'Cognitive-behavioral and Psychopharmacological Treatment of Delusional Symptoms: a preliminary report.' *Behavioural Psychotherapy,* 11, 50-61.

Harrison, G., Hopper, K. Craig, T. et al., (2001). 'Recovery from Psychotic Illness: a 15- and 25-year international follow-up study.' *British Journal of Psychiatry*, 178, 506–517.

Hogarty, G.E., Anderson, C.M., Reiss, D.J., et al., (1991). 'Family Psychoeducation, Social Skills and Training, and Maintenance Chemotherapy in the Aftercare Treatment of Schizophrenia: II. Two-year effects of a controlled study on relapse and adjustment.' *Archives of General Psychiatry*. (48), 340–347.

Hole, R.W., Rush, A.J. and Beck, A.T., (1979). 'A Cognitive Investigation of Schizophrenic Delusions.' *Psychiatry* 42, 312–319.

Jones, C. et al. (2004), 'Cognitive Behaviour Therapy for Schizophrenia.' Cochrane Schizophrenia Group, 18 October 2004.

Jones, C., Hacker, D., Meaden, A., Cormac, I. and Irving, C. B. (2011). 'Cognitive Behaviour Therapy versus Other Psychosocial Treatments for Schizophrenia', *Cochrane Database of Systematic Reviews*, Issue 4. Art. No.: CD000524.

Karon, B. P. (2003). 'The Tragedy of Schizophrenia without Psychotherapy.' *Journal of the American Academy of Psychoanalysis and Dynamic Psychiatry*, 31(1): 89-118.

Kemp, R., Haward, P., Applewhaite, G., Everitt, B. and David, A. (1996). 'Compliance therapy in psychotic patients: randomised controlled trial.' *British Medical Journal*, 312, 345-9.

Kingdon, D.G., and Turkington, D., (1991). 'The Use of Cognitive Behaviour Therapy with a Normalising Rationale in Schizophrenia.' '*Journal of Nervous and Mental Disease,* 179, 207–211.

Kingdon, D.G. and Turkington, D. (1994). *Cognitive-Behavioural Therapy of Schizophrenia*. Hove, UK: Lawrence Erlbaum.

Kuipers, E., Garety, P., Fowler, D., et al. (1997). 'London-East Anglia randomised controlled trial of cognitive behavioural therapy for psychosis. I. Effects of the treatment phase.' *British Journal of Psychiatry*, 171, 319-327.

Kuller, A. M. et al., (2010). 'Cognitive Behavioral Therapy and Schizophrenia: a survey of clinical practices and views on efficacy in the United States and United Kingdom.' *Community Mental Health Journal*, 46(1).

Leff, J. P., Kuipers, L., Berkowitz, R., Eberlein-Fries, R., and Sturgeon, D., (1982). 'A Controlled Trial of Social Intervention in Schizophrenia Families.' *British Journal of Psychiatry* (141), 121–134.

Lecomte, T., Leclerc, C., Corbiere, M., Wykes, T., Wallace, C. J., and Spidel, A. (2008). 'Group Cognitive Behavior Therapy or Social Skills Training for Individuals with a Recent Onset of Psychosis.' *Journal of Nervous and Mental Disease*, 196(12), 866-875.

Lehman et al., (*2004*). 'Practice Guideline for the Treatment of Patients with Schizophrenia' in *The American Journal of Psychiatry*, 161, 1–56 (35).

Lynch D., Laws, K. R. and McKenna, P. J., (2010). 'Cognitive Behavioural Therapy for Major Psychiatric Disorder: does it really work? A meta-analytical review of well-controlled trials', *Psychological Medicine* 40, 9–24.

Malik, N., Kingdon, D., Pelton, J., Mehta, R. and Turkington, D. (2009). 'Effectiveness of Brief Cognitive-Behavioral Therapy for Schizophrenia Delivered by Mental Health Nurses: relapse and recovery at 24 months.' *Journal of Clinical Psychiatry*, 70, 201–207.

Meichenbaum, D. and Cameron, R. (1973). 'Training Schizophrenics to Talk to Themselves: a means of developing attentional controls.' *Behavior Therapy* (4), 515–534.

Milton, F., Patwa, V. K., and Hafner, R. J. (1977). 'Confrontation vs. Belief Modification in Persistently Deluded Patients.' *British Journal of Medical Psychology,* 51*,* 127–130.

Morrison, A. P., Haddock, G. and Tarrier, N. (1995). 'Intrusive Thoughts and Auditory Hallucinations: A cognitive approach. *Behavioural and Cognitive Psychotherapy*, 23, 265–280.

Morrison, A.P., (1998). 'Cognitive Behaviour Therapy for Psychotic Symptoms of Schizophrenia.' in N. Tarrier, A. Wells, G. Haddock, eds. *Treating Complex Cases: The Cognitive Behavioural Therapy Approach*. London, UK: Wiley, 195–216.

Morrison, A. P., (2001). 'The Interpretation of Intrusions in Psychosis: An Integrative Cognitive Approach to Hallucinations and Delusions.' *Behavioural and Cognitive Psychotherapy*, (29), 257–276.

Mueser, K. T., Corrigan, P. W., Hilton, D., Tanzman, B., Schaub, A., Gingerich, S., et al. (2002). 'Illness management and recovery for severe mental illness: A review of the research.' *Psychiatric Services* 53, 1272–1284.

Mueser, K. T., Corrigan, P. W. et al., (2004). 'Illness Management and Recovery: a review of the research.' *Focus* 2(1), 34–47.

NICE (National Institute for Health and Clinical Excellence), (2002). *Schizophrenia: Core interventions in the treatment of schizophrenia in primary and secondary care*. London: Department of Health.

NICE (National Institute for Health and Clinical Excellence), (2010). *Schizophrenia: The NICE Guideline on Core Interventions in the Treatment and Management of Schizophrenia in Adults in Primary and Secondary Care*. The British Psychological Society & The Royal College of Psychiatrists.

Nuechterlein, K. and Dawson, M. E. (1984). 'A Heuristic Vulnerability-Stress model of Schizophrenia.' *Schizophrenia Bulletin*, (10), 300–12.

Olfson, M., Marcus, S. C., et al., (2009). 'Treatment Patterns for Schizoaffective Disorder and Schizophrenia Among Medicaid Patients.' *Psychiatric Services*, 60(2), 210–216.

PORT (The Schizophrenia Patient Outcomes Research Team)(1998). *At Issue: translating research into practice*., Rockville, MD: Agency for Healthcare Research and Quality.

PORT, (2004). 'Updated Treatment Recommendations.' Rockville, MD: Agency for Healthcare Research and Quality.

PORT, (2010). 'Updated Treatment Recommendations.' Rockville, MD: Agency for Healthcare Research and Quality.

Sensky, T., Turkington, D., Kingdon, D., et al**.,** (2000**).** 'A Randomized Controlled Trial of Cognitive–Behavioural Therapy for Persistent Symptoms in Schizophrenia Resistant to Medication.' *Archives of General Psychiatry*, 57, 165– 172.

Sherman, L. W., Gottfredson, D., MacKenzie, D., Eck, J., Reuter, P., and Bushway, S., (1997). 'Preventing crime: what works, what doesn't, what's promising. A report to the United States Congress.' Washington, D.C.: National Institute of Justice.

Sullivan, H. S. and Mullahy, P., (1947). *Conceptions of Modern Psychiatry*. Washington: W. A. White Psychiatric Foundation.

Tai, S. and Turkington, D., (2009). 'The Evolution of Cognitive Behaviour Therapy for Schizophrenia: Current Practice and Recent Developments.' *Schizophrenia Bulletin* 35(5), 865–873.

Tarrier, N., Harwood, S., Yusupoff, L., Beckett, R., and Baker, A. (1990). 'Coping Strategy Enhancement (CSE): a method of treating residual schizophrenic symptoms.' *Behavioural Psychotherapy,* 18, 283–293.

Tarrier, N., (1992). 'Psychological Treatment of Schizophrenic Symptoms.' in D. Kavanagh, ed. *Schizophrenia: An Overview and Practical Handbook*. London, UK: Chapman & Hall.

Tarrier, N., Beckett, R., Harwood, S., Baker, A., Yusupoff, L., and Ugarteburu, I., (1993). 'A trial of Two Cognitive-behavioural Methods of Treating Drug-resistant Residual Psychotic Symptoms in Schizophrenic Patients: I. Outcome. *British Journal of Psychiatry,* 162, 524–532.

Tarrier, N. and Wykes, (2004). *Behaviour Research and Therapy* (42), 1377–1401.

Turkington, D., and John, C. (1994). 'Cognitive Behaviour Therapy of Schizophrenia: the amenability of delusions and hallucinations to reasoning.' *British Journal of Psychiatry,* 164, 581–587.

Turkington, D. and McKenna, P., (2003). 'Is Cognitive-Behavioural Therapy a Worthwhile Treatment for Psychosis?'. *British Journal of Psychiatry*, 182, 477–479.

Turkington, D. et al. (2006). 'Cognitive-Behavioural Therapy for Schizophrenia: A Review.', *Focus* 4(2), 223–233.

Turkington, D., Sensky, T., Scott, J., et al., (2008). 'A Randomized Controlled Trial of Cognitive–Behavioural Therapy for Persistent Symptoms in Schizophrenia: a five-year follow-up.' *Schizophrenia Research*, 98, 1–7.

Watts, E N., Powell, G. E. and Austin, S. V. (1973). 'The Modification of Abnormal Beliefs.' *Behaviour Journal Medicine and Psychology,* 46*,* 359–363.

Weiden, E.J., Mott, T. and Curcio, N., (1995). 'Recognition and Management of Neuroleptic Noncompliance.' in: C.L. Shriqui, H.A. Nasrallah, eds., *Contemporary Issues in the Treatment of Schizophrenia*. Washington, DC: American Psychiatric Press, 411–434.

Wright, J.H., Turkington, D., Kingdon, D. and Ramirez Basco, M. (2009). *Cognitive-Behaviour Therapy for Severe Mental Illness: an illustrated guide*. American Psychiatric Publishing, 2009.

Yusupoff, L. and Tarrier, N. (1996). Coping strategy enhancement for persistent hallucinations and delusions. In G. Haddock, P. D. Slade, eds., *Cognitive-Behavioural Interventions with Psychotic Disorders*, London, UK: Routledge, 71–85.

Zubin, J. and Spring, B., (1977). 'Vulnerability: a new view on schizophrenia.' *Journal of Abnormal Psychology*, 86(2), 103–126.

CHAPTER 4 Early intervention for schizophrenia

4.1 Summary

In schizophrenia, a psychotic episode is characterised by a loss of contact with reality. Prompt treatment of episodes of psychosis has been the standard approach to care in most countries for many years. However, the language used in regard to the timing of this care and the different types of treatment can vary and, in some cases, add confusion to the discussions around treatment options. In this case study, we define two forms of 'early intervention' in the treatment of a psychotic episode that correspond to different stages of schizophrenia.

The *prodromal* stage of schizophrenia starts with functional deterioration and progresses to psychotic symptoms. We define early intervention in the prodromal stage as community-level detection efforts and different kinds of treatment to prevent onset of a psychotic episode and decrease morbidity from schizophrenia. We refer to these in this case study as *prodromal interventions.* Schizophrenia's *first episode* stage follows the first psychotic episode. We define early intervention for the first episode stage as a tailored intervention for first psychotic episodes that focuses on detection and prompt treatment and differs from standard care for psychotic episodes. We refer to these types of interventions as *first episode interventions.*

Some studies have examined tailored interventions for a first psychotic episode, which aim to treat a psychotic episode at any point, regardless of whether it was a first episode or one of many. These tailored, first episode interventions have been shown to lead to an improvement in treatment response and long-term outcomes. However, there have not been many randomised control trials showing a causal link between a specific tailored first episode intervention and improved outcomes.

In addition to reaching people after onset of psychosis and the occurrence of a first episode, in the last ten years there have been efforts to reach individuals with early intervention and treatment in the prodromal stage. Though this is still an emerging area, there are some studies, including five randomised controlled clinical trials, which have demonstrated the potential effectiveness of prodromal interventions. Nonetheless, many would argue that the evidence base is not considered strong and there are real debates in the literature and within the schizophrenia research community about the nature and robustness of the evidence for the effectiveness of prodromal interventions and first episode interventions.

Due to this lack of clarity over the strength of the evidence base for the effectiveness of either form of 'early' intervention, the practice guidelines in the United States, England and Canada vary on the degree to which they promote early intervention, either at the first episode or prodromal phase. In the United States, the latest American Psychiatric Association (APA) practice guidelines for the treatment of schizophrenia mention the importance of providing treatment as early as possible during the first episode stage but do not explicitly recommend a specific tailored treatment approach for a first psychotic episode or early intervention during the prodromal stage. In England, the current National Institute for Health and Clinical Excellence (NICE) guidelines on schizophrenia recommend a full range of treatments for the first episode stage but not specific tailored approaches for first episodes, while noting the lack of evidence for early intervention during the prodromal stage. Similarly, Canada's Treatment of Schizophrenia clinical practice guidelines describe the importance of intervening early for those in the first episode stage and acknowledge the need for more studies to determine the effectiveness of early intervention during the prodromal stage. Internationally, in 2004 the World Health Organization (WHO) and the International Early Psychosis Association (IEPA) jointly issued a declaration focused on the importance of intervention for early psychosis. The following year IEPA published international clinical practice guidelines for early psychosis. Individual countries such as Australia and New Zealand have also developed early psychosis guidelines.

There are clear challenges for the full implementation of early intervention services for both the first episode and prodromal stages. Though the guidelines recognise the importance of providing treatment as early as possible and recommend intervention at the first episode stage, they do not identify a specific tailored approach for early intervention in the first episode stage. Further, none of the guidelines recommend prodromal interventions. Overall, there is a need for a clear and coordinated research strategy to further develop the evidence base for specific tailored interventions for the first episode stage and early intervention for the prodromal stage. England is beginning to develop this, but in countries without a nationalised health service where mental health interventions are coordinated with other care, the implementation of such a strategy may be challenging and a real barrier to full implementation and further research.

4.2 Case study scope

Early intervention as it relates to psychotic episodes in schizophrenia has different meanings depending on the context. This has led to some confusion as to what it means. For the purposes of this case study, we are distinguishing between early intervention in the first episode stage, which we call first episode intervention, and early intervention in the prodromal stage, which we refer to as prodromal intervention. We define early intervention in the prodromal stage as community-level detection efforts and treatment to prevent onset of a psychotic episode and decrease morbidity from schizophrenia. We define early intervention during or after the first episode stage as a tailored intervention for first psychotic episodes that focuses on detection and prompt treatment and differs from usual care for any psychotic episode.

For both stages, the focus on tailored interventions delivered as early as possible emerged from the recognition by schizophrenia researchers that early diagnosis and treatment is critically important. While this case study originally sought to focus on prodromal interventions and treatments prior to onset of psychosis and diagnosis of schizophrenia, both prodromal and first episode interventions developed concurrently, with the streams of research coming together and moving apart over time. As such, it is important to consider the advances in research and tailored treatment for the first episode stage that both informed and influenced developments in studies of prodromal intervention.

This case study therefore addresses research and treatment developments for both the prodromal and first episode stages, but does not aim to cover either field in its entirety. The developments highlighted are those which arose in the course of, and within the limitations of, our research, which included literature reviews, interviews with six experts in the US, UK and Canada and a critical peer review of this case study document by two international experts. In this case study, then, we aim to provide a comprehensive, but not necessarily exhaustive, account of key developments in the field of early intervention treatment and research for the prodromal and first episode stages.

The pathway to schizophrenia is not always straightforward, but could be described as starting with a premorbid stage, moving to a prodromal stage, and then progressing to the first episode stage. The premorbid stage is typically asymptomatic although there may be some motor, social or cognitive deficits. The early prodromal stage is characterised by functional deterioration, which is typically followed by onset of full-blown psychotic symptoms. During this prodromal stage, these symptoms progressively increase before the first episode. It is important to note, however, that not everyone with premorbid signs becomes prodromal, and not everyone with prodromal signs develops first episodes of psychosis. Regardless, the first episode stage has been identified as a 'critical period' in the course of schizophrenia (Birchwood et al., 1998). This recognition of the need to intervene at the first episode led to widespread adoption of practices to treat patients at this stage, and to the development of more tailored approaches to these first episode interventions.

Intervention after a first episode of psychosis is a secondary prevention approach meant to reduce the severity and duration of the disorder following the first episode. As schizophrenia research advanced, so did the understanding that treatment of the disease after the first episode could improve long-term outcomes for patients. For those in this first episode stage, the main component of a tailored intervention frequently involves detection and prompt treatment with antipsychotic medications, together with psychosocial treatments for those exhibiting psychotic symptoms. Thus, although treatment strategies are based on the same components of those used for established schizophrenia, clinical researchers have adapted these interventions for the first episode stage of schizophrenia (eg Miller and Mason, 2009; McGorry et al., 1996). Overall, the two aspects of first episode intervention that distinguish it from standard care are early detection and phase specific treatment (ie treatment tailored to a specific phase of schizophrenia) (Marshall and Rathbone, 2010).

While the field of early intervention research has grown in the past two decades, it is predicated on wider developments in the field of schizophrenia research that began making

headway in the 1980s, when the whole field started to coalesce. In particular, as is discussed in more detail elsewhere in the Mental Health Retrosight study, the whole field of schizophrenia research was affected by advancements in the understanding of the psychobiology of schizophrenia and the growing awareness that schizophrenia was caused by underlying biological mechanisms in the brain. Other case studies in the wider Mental Health Retrosight study – such as Cohen's work on PET scanning, Seeman's work on the role of dopamine receptors, Johnstone and Crow's Northwick Park work (see below), and the World Health Organization's (WHO) broad support of work to understand the outcomes from first episodes of schizophrenia – are only one part of this broader story (Pollitt et al., 2013). In particular, work done at the National Institute of Mental Health (NIMH), as well as Lieberman and Kane's work at the Long Island Jewish Medical Center in New York, made important contributions to the understanding of the relationship between biological and physiological responses, and the outcomes of the disease. Notably, they found that the one-year remission rate for schizophrenia was close to 80%. Kane also made important contributions to the way treatment could affect relapse, showing that different dosing strategies had varied effects on outcomes. All of this background laid the foundation for continued developments in the field and many of the studies described in this case study built on this momentum in some way.

Three categories of studies of early treatment with antipsychotic medications provide evidence related to the effectiveness of first episode interventions; however, these studies were largely conducted before first episode, or for that matter prodromal, interventions were conceptualised as a treatment approach.

- Epidemiological studies examined changes in incidence related to introduction of different treatment approaches. While some of these studies show declining incidence of schizophrenia over the last 60–70 years, there are challenges to estimating these incidence rates such as changes over time in how schizophrenia is diagnosed (Wyatt and Henter, 2001).
- Mirror-image studies, those which compare similar patients before and after the introduction of antipsychotics, indicate improvements in the course of disease after the introduction of antipsychotic medications in the 1950s (Wyatt and Henter, 2001).
- Delayed intervention studies compared a treatment group who received early intervention with antipsychotics to a wait list control group who received delayed treatment. These studies generally found that delaying intervention led to poorer outcomes, although the evidence was not clear cut (Wyatt and Henter, 2001). In the early 1980s, studies in Australia and England found a link between delays to treatment and poor outcomes (Johnstone et al., 1986).

Through these and other studies, the duration of untreated psychosis has been established as a predictor of outcomes for first episode schizophrenics. But more crucially, all the studies contributed to a better appreciation of the idea that early intervention, of any type, can lead to improvement in outcomes for the patient and their families. Thus, the results of these studies motivated, in part, the development of both first episode and prodromal intervention approaches and led to additional studies to determine the effectiveness of these intervention treatments on outcomes (Malla et al., 1999; Chen, 1999). On this basis, and concurrently with research and advances in treatment for tailored interventions in the

first episode stage, researchers in the field began to examine early intervention in the prodromal stage. While treatment of patients with first episodes of psychosis was considered standard care, the evidence is mixed about the effectiveness of early intervention before this first episode stage.

The studies and other key events in the development of first episode and prodromal interventions are detailed below. Many of the clinical service programmes emerged from research or academic activities and both the first episode and prodromal intervention services and research studies were funded through public mental health service systems. Figure 1 provides a timeline of key events in the development of first episode and prodromal intervention and Table 1 outlines these events in a tabular format. Both the figure and table distinguish early intervention in the prodromal stage from early intervention in the first episode stage when relevant.

4.3 Timeline of key events

Year	Event/Study
1979–1990	Northwick Park Study of early intervention in the **first episode** stage (England)
1984–1988	Buckingham study of early intervention in the **prodromal** stage (England)
1987–1991	Bonn early recognition study of early intervention in the **prodromal** stage (Germany)
1992	Early Psychosis Prevention and Intervention Centre (EPPIC) programme for early intervention in the **first episode** stage established (Australia)
1992–1997	Research based clinical programs for early intervention in the **first episode** stage established in Calgary, Toronto, London and Halifax (Canada)
1995	Birmingham Early Intervention Service for young people in the **first episode** stage established (England)
1995	Initiative to Reduce Impact of Schizophrenia (IRIS) formed (England) (primarily relevant to both first episode stages)
1996	First international early intervention (both first episode and prodromal stages) conference held in Melbourne (Australia)
1994	Personal Assessment and Crisis Evaluation Service (PACE) clinical service for early intervention in the **prodromal** stage established (Australia)
1997–2003	PRIME early intervention study during the **prodromal** stage (United States)
1997–2000	Treatment and Intervention in Psychosis Study (TIPS) of **first episode** stage

	began (Norway)
1997	Follow-up early intervention for the **first episode** stage conference held in Stratford-upon-Avon (England)
1997	International Early Psychosis Association (IEPA) founded (Australia)
1999	Canada Mental Health Association early psychosis intervention project began (Canada) (relevant to both first episode and prodromal stages)
1999	Early intervention in the **first episode** stage referenced in National Service Framework (NSF) for Mental Health (England)
2000	Second international early intervention for the **first episode** stage conference held in New York
2001	Mental Health Policy Implementation Guide prioritised the development of early intervention teams for **first episode** stage (England)
2001	OPUS study of **first episode** stage reported first data (Denmark)
2001	Lambeth Early Onset (LEO) study of early psychosis services for **first episode** stage began (England)
2001	Several early psychosis programmes and research efforts for **first episode** stage launched in different countries, including Hong Kong, Singapore and Switzerland.
2002	RETHINK established out of the National Schizophrenia Fellowship to fund work in early interventions services (England) (relevant to both first episode and prodromal stages)
2002	Third early intervention for the **first episode** stage international conference held in Copenhagen, Denmark
2002	IRIS and the World Health Organization (WHO) developed standards of care for early psychosis (England) in the first episode stage)
2002	**First Episode** Research Network (FERN) formed (England)
2004	WHO and IPEA jointly issued a declaration on early intervention for psychosis in the first episode stage
2004	National Early Intervention Development Programme created to support early intervention policy development (England)

2006	National EDEN project findings of **first episode** stage reported (England)
2007	Omega-3 fatty acid intervention trial of **prodromal** stage published (Austria)
2007	Early Intervention in Psychiatry journal launched by IEPA (relevant to first episode and prodromal stages)
2007	Early Detection and Intervention Evaluation Trial for **prodromal** stage published findings (England)
2009	Recovery After an Initial Schizophrenia Episode (RAISE) research project of **first episode** stage began (United States)
2010	National Early Intervention Development Programme concluded with a conference in Birmingham (England) (relevant to both first episode and prodromal stages)

4.4 Narrative

1979–1990 Northwick Park study of first episode interventions (England)

The Northwick Park Study in England was one of the first to look into the management of first episode illness in schizophrenia. At the time of the study, not all first episode patients would go on to receive prophylaxis treatment; some clinicians only offered long term prophylaxis after a second episode. Therefore, the initial aims of the study were to examine the prophylactic use of neuroleptic drugs after the first episode in order to prevent relapse. Multiple studies had examined the continued use of neuroleptic drugs to prevent relapse, but none had looked specifically at the effects following the first episode. The team expected to find a group of patients who were less likely to relapse, and therefore would not need to take neuroleptic drugs on a continued basis in order to prevent relapse. They also expected to be able to identify characteristics of this group of patients which would then guide future treatment.

The study participants were referred from nine medical centers after a first episode; all received medication following the first episode. Interestingly, the findings did not yield the expected results, in that the investigators were not able to identify a non-relapsing patient group. Instead, the findings of the study pointed to the difficulty in examining and documenting patients with a first psychotic episode. In particular, the study highlighted the long delay which can occur between onset of psychotic symptoms and admission to hospital, and the importance of minimising the treatment delay many patients experienced. The study also pointed to the serious flaws in services provided to those in the first episode and early stages of schizophrenia (Johnstone et al., 1986). Funding for the study came from the Medical Research Council as Northwick Park was located at one of the MRC research centres.

Overall, the Northwick Park study shaped the trajectory of further research in the area of first episode interventions by highlighting that treatment delay in schizophrenia was important to outcomes. In other words, the duration of untreated psychosis could have a significant impact on patient outcomes. Many of the studies and programmes discussed below cite this study as a basis for their work.

1984–1988 Buckingham study of early intervention in the prodromal stage (England)

The Buckingham study (1984–1988) in England was the first study to focus on early detection of psychosis during the prodromal period (Falloon, 2003). Considered one of the first prodromal intervention programmes, the service evaluated by the study was developed in a rural England community with primary health care services but without conventional mental health services system. Mental health services were provided instead through the GP practices and through a system of family-based care with people who would otherwise have been hospitalised being treated in their own homes. The researchers, Ian Falloon and Grainne Fadden, had hoped to conduct a rigorous controlled trial to establish an evidence base for intervention in the prodromal stage but lacked the necessary funding from the local health authority to do this (Falloon et al., 1996; Falloon et al., 1998). Funding for the study overall was provided by the Aylesbury Vale District Health Authority, whose senior management supported the project, and Buckinghamshire Social Services. These public agencies had funds from the sale of traditional psychiatric institutions to reinvest into local services. Instead of building new mental health facilities with hospital beds, Falloon wanted to develop a genuine community service and the idea for the study was born. It was also inspired by the success of Falloon's work in the US on psychosocial family therapy interventions. He wanted to introduce a similar model of service, but in a more integrated way, in the UK. The evaluation component was supported by funds from the Mental Health Foundation, the Oxford Regional Research Fund, and the Department of Health. Towards the end of the study, a training and dissemination project was developed through funding from the Research and Development in Psychiatry.

The objective of this pilot study in Buckingham was to test the feasibility of integrating mental health care with the physical (primary) health care system in order to reduce treatment delays in schizophrenia. The pilot study developed a ten-question screening checklist and then trained general practitioners to use the checklist to detect prodromal symptoms. Those who screened positive received a referral to a mental health services team for an assessment and treatment. The treatment consisted of low-dose medication, family education about schizophrenia, and social skills training with a focus on stress management. The results of the study showed a dramatic reduction in the incidence of schizophrenia in the community (from 7.4 per 100,000 to 0.75 per 100,000 total population) (Larsen et al., 2001). While the study was limited because it did not discern whether schizophrenia had been avoided or delayed, these results affected research and clinical practice in the field by reinforcing the importance of early detection and management of schizophrenia.

1987–1991 Bonn early recognition study of interventions in the prodromal stage (Germany)

Contemporaneous with the Buckingham Study, the Bonn early recognition study in Germany was designed to test whether the development of schizophrenia could be predicted from prodromal symptoms using an assessment tool. The tool was designed to assess the basic symptoms (ie subjective distrubances that are perceived internally by the affected person) and determine whether a patient is at high risk of developing psychosis based on the results. This basic symptoms approach was the first conceptualisation of the prodromal stage. The tool developed in Bonn provided a more descriptive assessment of the different features of the prodromal stage than the more widely used Perceptual Aberration Scale and Thought Disorder Index. At the time of the study, the Bonn Scale for the Assessment of Basic Symptoms was used in Germany as well as other European countries and Japan. Using this scale, the study examined early experiences in non-schizophrenic patients to determine the transition rate to psychosis and the predictors of this transition (Klosterkotter, 1997). The study focused on patients in the prodromal stage who were referred to a university-based psychiatric clinic for diagnosis from 1987–1991. The patients were referred for additional diagnosis and then follow up eight years later. At follow up, the patients were assessed to determine whether they had developed schizophrenia. The results found that 58 percent of the patients developed schizophrenia with certain baseline symptoms predictive of this transition.

The contribution of the Bonn study (as well as similar studies from Australia and the United States) was in the development of tools to assess prodromal symptoms and test their ability to predict later schizophrenia (McGlashan 2003). In particular, this study differed from other intervention studies of the prodromal stage because of its focus on the means to assess the 'basic symptoms' associated with schizophrenia (de Koning et al. 2009). Subsequently (see below), these tools were also used in clinical trials to test interventions in the prodromal stage.

1992 EPPIC programme for intervention in the first episode stage established (Australia)

The following year, the Early Psychosis Prevention and Intervention Centre (EPPIC) programme in Melbourne, Australia was established as an integrated, comprehensive care service for youths aged 15–24 who have emerging, psychotic disorders. The EPPIC service itself was created with health service specific funding from the Victorian State Government. The Early Psychosis Research Centre was funded by the Victorian Health Promotion Foundation through a research programme grant titled 'Preventive Strategies in Early Psychosis'. Additional support came from the Australian National Health and Medical Research Council Schizophrenia Research Unit and the US-based Stanley Foundation. There were synergies between the two main funding sources within the Australian state of Victoria which helped to establish the close relationships between the research and the service itself. Patrick McGorry was the driving force behind the development of the EPPIC programme.

The origins of EPPIC date to 1984 when a research and clinical focus on first episode and recent onset of psychosis patients was established at the Aubrey Lewis Unit and Recovery Program at the Royal Park Hospital in Melbourne, Australia. The unit initially had ten

beds for acute patients and the experiences and insights gained from this early clinical focus led to a better understanding of the patients' clinical needs and the limitations of standard care. More importantly, it pointed to the 'possibilities of a broader, more preventive approach' (McGorry 1996, 309). In 1986 the scope of the ward was expanded to include more beds and a phase specific psychosocial recovery approach and in 1990 a common unit shared between the Aubrey Lewis Unit and the Nightingale Psychosocial Recovery Program was opened. The ward was established to provide an atmosphere that was more conducive and supportive to the challenges faced by the young early psychosis patients and their families.

On the strength of the experiences in the hospital, the community-based EPPIC programme was launched in 1992. Around this time, there was also growing evidence in the field (as detailed above and below) which supported the idea that more effective secondary prevention was important, if not crucial, for patient outcomes (McGorry 1996). This case was made in detail in a paper by McGorry and colleagues which states,

> a realistic secondary preventive approach would involve strategies that first reduce the duration of untreated psychosis and second optimize the management of the disorder during the early years after detection. Such an approach would be expected to result in a more cost-effective service for young people at this stage of illness. (McGorry 1996, 306)

The EPPIC programme offered a number of community-based services linked with a specific early psychosis inpatient unit and represented a shift in focus from the pure hospital setting to the wider community. The programme was a secondary prevention intervention to improve early detection and provide specialised treatment for early psychosis and treatment-resistant psychosis (Larsen et al. 2001). Patients were identified for the programme through a mobile early detection team, the Early Psychosis Assessment Team (EPAT). The mobile team responded to referrals, conducted assessments, and enrolled patients in the programme. It also conducted community education activities to raise awareness. EPAT also had methods for dealing with the sensitivities of the individual and families once the assessment phase for diagnosing schizophrenia began. Support and information was provided at each phase of assessment and the assessments themselves were carried out in the least threatening environments possible. Once enrolled, the patient was assigned a case manager to coordinate and provide treatment. The EPPIC programme also had an inpatient unit for those patients who had severe symptoms that could not be handled in the outpatient setting. In 1994, the programme was further enhanced when the Personal Assistance and Crisis Evaluation (PACE) clinic opened within the EPPIC clinic to serve those people who are 'at risk' of psychosis (Larsen et al. 2001. See below for a description of the PACE clinic). In 1996, an initial evaluation of the effectiveness of the EPPIC programme was published. This was a naturalistic longitudinal study with multidimensional outcome measures for effectiveness. The sample comprised 51 patients who presented to EPPIC with a first episode of psychosis over an eight-month period in 1993. The control group received pre-EPPIC care at the Royal Park Hospital prior to the opening of EPPIC. Though these patients received a high quality of care, it was short-

term with poor follow through. The study found some conflicting data with some evidence of a trend towards lower duration of untreated psychosis in the EPPIC sample (though it was not significant), significantly fewer admissions and negative symptoms, and significantly better functioning.

Overall, the methods used in the EPPIC programme utilised new mechanisms for diagnosis and approaches to treatment for the first episode stage. A core aim of EPPIC was to develop a psychiatric health system with a strong emphasis on early detection and early treatment of first episode psychosis (Larsen et al. 2001). Since its founding, the EPPIC service has evolved to cover a broader range of emerging mental disorders in the age group via the Centre for Young People's Mental Health (1996) and Orygen (2002–present). EPPIC has also created a national system of youth friendly primary care called Headspace.

1992–1997 Research based clinical programs for intervention in the first episode stage established in Calgary, Toronto, London and Halifax (Canada)

In the early to mid-1990s in Canada, those working in the field also began to understand the importance of the first episode and think about early involvement at this stage. Four programmes developed from 1992–1997. The programmes varied depending on funding. At the time, none of the provincial governments considered themselves to be funding interventions for the first episode stage. These were clinical service programmes based at academic hospitals and funded through the provincial governments. These programmes conducted some research in conjunction with the clinical services being offered.

- The programme at the University of Toronto started first in 1992 at the Clark Institute of Psychiatry, a teaching hospital of the University of Toronto Faculty of Medicine. In 1998 it merged with other centres to become the Centre for Addiction and Mental Health (CAMH). CAMH is now Canada's largest publicly funded teaching hospital for addiction and mental health with a large outpatient clinic, an inpatient treatment programme, and a community-based rehabilitation programme. The Toronto first episode programme was designed to improve care through innovative research and the development of clinical and research experts, including medical students, psychiatry residences, post-doctoral fellows, and other mental health professionals. The programme provided multidisciplinary assessment and case management to individuals 18–45 years of age who had experienced a first episode of psychosis.
- The programme at Dalhousie University in Halifax, Nova Scotia began in 1995 offering early intervention for the first episode stage through its clinical trials. This programme had limited funding in its early days and ultimately focused more on education of clinicians. The programme provided psychopharmacological treatment, psychoeducation, peer support, and community referrals to patients between the ages of 12 and 54 who had experienced a non-affective first episode of psychosis.
- In London, Ontario, the province-wide Prevention and Early Intervention Program for Psychosis (PEPP) began in 1997 as a clinical initiative of the government. It was led by the five academic centres in Ontario with first episode programmes. While the PEPP grew over time, it was limited by funding issues. The programme

provided assertive case management to patients 16 to 50 years of age who had experienced a non-affective first episode of psychosis.

- In 1997, the University of Calgary set up a first episode early intervention programme within the hospital's existing clinical outpatient programme. The new clinical service was funded by Alberta Mental Health. Alberta Mental Health had an unexpected surplus at the time and decided to have a competition to provide funds for something new and different. Calgary's new first episode programme included a psychiatrist, psychologist, case managers and family support. The Calgary programme was modeled after the EPPIC programme in Australia with case management, individual family and family group work and individual cognitive-behavioral therapy for patients 16 to 50 years of age with a non-affective first episode of psychosis.

The leaders of these four programmes all knew each other and communicated about their respective programmes. The first episode intervention research and clinical practice community in Canada was large compared to other countries, particularly the US, with far more research undertaken here than in many other countries. These programmes are still active although not research-funded. Currently, these and other first episode intervention programmes in Canada are funded at the provincial level. First episode intervention programmes are widespread in Canada, particularly in the province of Ontario and the cities of Vancouver and Montreal.

1995 Birmingham Early Intervention Service for young people in the first episode stage established (England)

Established in 1995, the Birmingham Early Intervention Service serves young people experiencing the first episode of psychosis. This service was established by Professor Max Birchwood, a clinician and academic working in Birmingham, to examine why so many young people were being admitted to the psychiatric wards and determine whether it was possible to identify schizophrenia early. Two years earlier, one of the leaders of the Northwick Park study (Fiona MacMillan) had moved to Birmingham and connected with Birchwood. Together they wrote a paper on early intervention and schizophrenia that described the empirical evidence base for early intervention during the first episode stage and the importance of services at this stage (Birchwood and MacMillan 1993). The paper is cited in many articles discussing the importance of intervention in the first episode stage of schizophrenia. In addition to the synergies with MacMillan's work, Birchwood had also spend a period of sabbatical in Australia with McGorry and learning about the services and research efforts within the EPPIC and PACE programmes. This had an influence on Birchwood's thinking and the way the Birmingham service was established (Birchwood: Personal communication 2011).

Under Birchwood's direction (MacMillan left Birmingham in 1994 to join the North Staffordshire NHS Trust), the Birmingham first episode Early Intervention Service began running in 1995 and was funded through the reapplication of existing mental health service funds from the local National Health Service (NHS) trust. It was run out the Archer Centre which itself was opened in late 1990 as a Specialist Rehabilitation Centre providing intervention programmes for people suffering from long-term mental illnesses

and symptoms of schizophrenia and manic depression. It included a Recovery Programme for patients recovering from acute psychosis, individual sessions in learning how to control symptoms of psychosis, family education, support and intervention programmes and sessions, maintenance and monitoring services with a dedicated medical and nursing staff to provide long term drug therapies, individual and group sessions in daily living skills and social networking, and employment and preparation training. The Centre also had a teaching, research and evaluation component, the latter of which was supported by a grant from the West Midlands Regional Health Authority. Patients were referred to the Archer Centre's services from Northern Birmingham Community Mental Health Teams and then accepted into the centre after an assessment by a multi-disciplinary health team. In 1994, when MacMillan left, the Archer Centre closed and became the Birmingham Early Intervention Service.

In 2002, an Early Detection and Intervention Team was incorporated into the work of the Birmingham Early Intervention Service to provide assessment, intervention and psychological treatments to young people who have been identified as being at high risk of developing serious mental health problems. It was the first service of its kind in the UK with three treatment approaches: clinical services, mental health promotion activities and ongoing research and evaluation. The establishment of this service and the development of an evidence base to support its effectiveness through evaluations, lay the groundwork for future investment in early intervention services for the first episode stage across the UK (see the descriptions of the 1999 Mental Health Policy Implementation Guide and the 2004 Early Intervention Development Programme below). One particularly important driver of this uptake into policy was that Sir David Nicholson, a former Chief Executive of NHS services in Birmingham, went on to have a senior position at the national Department of Health and became a key champion for the implementation of early intervention services across the country.

1995 Initiative to Reduce Impact of Schizophrenia (IRIS) formed (England)

Founded in 1995, the Initiative to Reduce the Impact of Schizophrenia (IRIS) focuses on developing and supporting the implementation of intervention programs for the first episode stage within England's National Health Service. It was driven by a small group of clinicians and academics in the Birmingham area coming together, primarily motivated by the passion of a local general practitioner, Dr David Shiers, whose daughter Mary had schizophrenia. Mary was under the care of Fiona MacMillan at the time. Joining forces with Birchwood, MacMillan, Smith and Shiers, and with the support of a local policymaker in the West Midlands Health Trust, Antony Sheehan, IRIS was launched.

IRIS initially focused on working with young people living in the West Midlands. It was essentially unfunded and worked to raise awareness and implement local services for young people after a first episode of psychosis. IRIS worked to develop a programme that expanded upon the first episode intervention work of Jo Smith, Max Birchwood, Fiona Macmillan and others in the West Midlands area. In 1998, Gráinne Fadden who had worked with Falloon in the Buckingham service (described above) moved to Birmingham to establish the region-wide Meriden Family Programme (Fadden and Heelis, 2011). She joined the group and supported the development of the family intervention component of

the work of IRIS. The work of the group was 'further encouraged' by interactions and intellectual exchanges with Professor Patrick McGorry in Australia, including a tour of his EPPIC clinic in 2001 and an earlier visit by McGorry to the West Midlands in 1994 (McGorry: Personal communication, 2012). In addition to articulating their thinking about how to improve services, those involved with IRIS conducted a retrospective study of all outpatients with a first episode of psychosis in Worcestershire over the previous three years. This combination of developing a service and having the audit and research to provide evidence it was needed proved important when it came to influencing national policy in the early 2000s (see below). Eventually, the toolkits and guidelines provided by IRIS about how to develop and implement first episode intervention services became the basis for the national guidelines (see below) and the launch of the National Early Intervention Development Programme (NEIDP).

In the early to mid 1990s, the founders of IRIS came across a group called the Institute for Research and Innovation in Social Services (IRISS) which was run by a university student affiliated with, and supported by, the National Schizophrenia Fellowship (see below). The inadvertent 'sharing' of names made the two groups realise they shared a common purpose and they joined forces in the mid-1990s and supported each other's initiatives. This partnership was to become crucial later on as early intervention for the first episode stage became embedded in mental health services in the UK.

1994 PACE clinical service for intervention in the prodromal stage established (Australia)

Also in the mid 1990s, the Personal Assessment and Crisis Evaluation Service (PACE), was established as an outgrowth of the EPPIC programme in Melbourne. The PACE clinic was the first to begin developing the ultra high-risk approach to prodromal intervention programs for the prodromal stage. The leader of PACE was Alison Yung, a psychiatrist within the EPPIC programme.

Starting in 1994 as part of the research programme of the Early Psychosis Research Centre, research on the prodromal stage focused on identifying and measuring prodromal symptoms since clinical trials of treatments during this stage were limited (McGlashan 2003). PACE's psychosocial treatment strategy focused on reducing stress, enhancing coping, and providing individual case management and support, stress management and problem solving. PACE drew attention to the differences between the threshold criteria for the psychotic, prodromal and non-psychotic states by developing the first early assessment tool to measure prodromal symptoms, called the Comprehensive Assessment of At-Risk Mental States (CAARMS). This structured diagnostic interview assessed positive and negative symptoms (as well as other symptoms like cognitive changes, behavioral changes, emotional disturbances) that can occur during the prodromal stage. The criteria for being at ultra-high risk are precisely defined in the CAARMS and there are thresholds for intensity, frequency and duration of the positive symptoms of psychosis and a precise definition of significant decrease in functioning (Yung 2005). The CAARMS was built on the experience developing the Royal Park Multidiagnostic Instrument for Psychosis, the work of Alison Yung (1995), the Comprehensive Assessment of Symptoms and History, and the Brief Psychiatric Rating Scale tools. The CAARMS was designed to assess

symptoms and signs of the first psychotic episode and was refined over the following nine years based on its use in PACE. In 2005 it was formally introduced in the literature, where it was found that the control group had significantly lower CAARMS scores than the ultra-high risk group and higher CAARMS scores were found to be significantly associated with onset of psychotic disorder. Moreover, the use of the CAARMS was similar to the use of existing methodologies in identifying ultra-high risk patients. Though CAARMS was published in 2005, its underpinning principles can be assumed to have been in development since the beginning of the PACE clinic and it was the basis and inspiration for the 1997 early Treatment and Intervention in Psychosis Study (TIPS; see below) developed by McGlashan who visited the PACE clinic in 1994.

A number of research efforts emanated from the PACE clinic. The research was funded in part by grants from Victorian Health Promotion Foundation (Melbourne), National Health and Medical Research Council (Canberra), Australian Research and Development Grants Advisory Scheme (Canberra), National Alliance for Schizophrenia and Depression (Great Neck, NY), Stanley Foundation (Muscatine, Iowa), Department of Human Services (Victoria), and Janssen-Cilag. An early evaluation of the service was published in 1996 which outlined the concepts and services behind the clinic. That article suggested that future research in the field needed to focus on several areas, including redefining the criteria for assessing high-risk patients in the prodromal stage (this was to become the CAARMS), a further research study of at-risk individuals and research into intervention in high-risk individuals. This latter area of research was ongoing at the clinic with a first area of research comparing the transition rates to psychosis in a group receiving psychosocial treatments and low-dose neuroleptics with that of a control group receiving no intervention. The second area of research was intended to compare the efficacy of the two treatment types when applied independently to the high-risk group.

The first randomised clinical trial for intervention with prodromal (or ultra-high risk, as referred to in the study) patients was conducted with PACE patients (1996–1999) and was published in 2002. The study compared the outcomes, as defined by progression to first episode psychosis, for two groups of ultra high-risk patients. There were 59 patients included in the trial. The patients were selected using the criteria that were further elaborated and developed into the CAARMS structured diagnostic tool. The treatment group received a combination of risperidone plus cognitive behavioral therapy, and the control group received supportive psychotherapy only. The main outcome measure was transition to psychosis. The data showed that significantly more people in the control group transitioned to psychosis by the end of the treatment phase. However, twelve months later this difference was no longer significant. The study was subject to some limitations related to its inability to identify those at imminent risk of psychosis (de Koning 2009).

1996 First international conference on early intervention for the first episode stage held in Melbourne (Australia)

In the midst of the burgeoning clinical and research work in England, Canada, Germany and Australia, the first international first episode early intervention conference was held in Melbourne in June 1996. Titled *Verging on Reality*, the conference focused exclusively on

early psychosis. Funding for conference came from Janssen-Cilag, a subsidiary of Johnson & Johnson, now known as Janssen EMEA.

The conference brought many of the main researchers in the field together before an international audience at an important time. The conference can be seen in hindsight as a galvanising force in the field. Aside from the Buckingham study and the EPPIC programme, other notable papers presented at the conference include that of Birchwood from the Birmingham Early Intervention Service who presented the 'critical period hypothesis'. Tom McGlashan[6] presented his work on brain imaging to try and understand if neurological changes could be detected in the prodromal stages of schizophrenia (McGlashan 1998). Other presenters at the conference highlighted in this case study included Falloon (Buckingham project: Falloon 2000), Larsen and Johannessen (future principal investigators in the TIPS study in Norway, see below. Johannessen 1998), and Addington (Canadian early intervention services for the first episode). A consensus statement on early intervention was developed at the conference and plans to form an international network (later to become the IEPA) began to take shape. A special issue of the June 1998 issue of the *British Journal of Psychiatry* was devoted to the proceedings.

The conference organisers noted a few key developments that were important to the field of first episode interventions, particularly in Australia. First, the rise of the evidence-based medicine paradigm seemed particularly important in driving research forward since it provided a strong base from which to develop intervention services. Second, governmental support had begun to play an important role in developing intervention services for the first episode stage. In Australia, support from Victoria's Psychiatric Services Branch of the Department of Human Services was considered crucial to the development of the theoretical underpinnings of the EPPIC programme. Also around this time in the mid-1990s, the Australian Mental Health Branch of the federal Department of Health and the National Mental Health Policy and Plan provided funding for a National Network which linked early psychosis programs around Australia. These networks helped with training and providing education/resource material to clinicians and the communities being served. In the late 1990s Australia also developed national early psychosis guidelines. More broadly, similar networks were forming in New Zealand and Scandinavia and the international network called the International Network for the Study and Treatment of Early Psychosis (later to become IEPA) was also beginning to take shape. Third, the developments in the field and the need for support came at a time of economic restraint and managed care (ie when an organisation such as a Health Maintenance Organization or an insurance company serves as an intermediary between the patient and the physician), which posed challenges to moving the field forward (McGorry 1998).

1997–2003 PRIME study during the prodromal stage (United States)

In the United States, the 1997–2003 industry-funded PRIME (Prevention through Risk Identification, Management, and Education) study involved the development of an assessment for prodromal symptoms and a randomised control trial at four clinics to

[6] See further details about PRIME and the TIPS study below for McGlashan's role in early intervention research.

examine the efficacy of early treatment with antipsychotic medication (Miller et al. 2003). Shortly after the CAARMS was developed by the PACE project, the PRIME team developed the Structured Interview for Prodromal Syndromes instrument based on the approach to ultra high-risk patients developed in the PACE study. Earlier research on the conversion rate to psychosis made the randomised control trial feasible (McGorry et al 2002).

The study was funded by an investigator-initiated grant from Eli Lilly with additional support from the authors' NIMH grants, one of which was a NIMH Senior Scientist Career Award (K05). According to one of the study's lead authors Eli Lilly funded the study because of the initial success of a prodromal clinic set up by Thomas McGlashan at Yale University. This clinic was initially funded through an Established Investigator Award which was awarded to McGlashan from the organisation North American Research into Schizophrenia and Depression (NARSAD). McGlashan was inspired to create the clinic because just prior he had travelled to Melbourne and met McGorry, Yung and colleagues and saw first-hand the work at the PACE clinic. Once the clinic was running, it became clear that he had a population of patients who were at different levels of psychosis and he wanted to see if they could prevent or delay onset. Eli Lilly was approached through personal contacts of McGlashan's and the study progressed from there. McGlashan invited the other three sites to join the study to increase sample size.

This was the first double-blind, placebo-controlled clinical trial to look at antipsychotic medications for prodromal symptoms. The objective of the study was to determine whether treatment with standard dosage of olanzapine would delay or prevent conversion to psychosis and reduce symptoms during the prodromal stage. Prior studies of antipsychotics in the prodromal stage had used lower than standard doses (McGlashan 2003). Patients in the study were randomised to receive olanzapine or a placebo. The treatment lasted for one year with a one-year follow up to assess symptoms. Participants in both groups also received a psychosocial intervention to address stress management and problem solving skills. The results of the study indicated that there was a non-significant trend toward delaying the conversion to psychosis for those young people with clear signs of early schizophrenia. However, the study had difficulty recruiting and retaining study participants which meant that it lacked statistical power to detect an intervention effect due to the low sample size.

1997 TIPS study of first episode stage began (Norway)

In 1997 the early Treatment and Intervention in Psychosis Study (TIPS) in Norway began. The TIPS study is one of the few controlled trials for first episode interventions. It was spear-headed by McGlashan (see PRIME study) and Jan Olav Johanessen. The inspiration for the study 'came out of the literature on reducing the duration of untreated psychosis of first episode schizophrenia.' (McGlashan: Personal communication, 2011). The study was funded by the Norwegian National Research Council, the Norwegian Department of Health and Social Affairs, the Rogaland County Department of Health and Social Affairs, the NARSAD Distinguished Investigator Award and an NIMH K-award for Dr McGlashan. The initial study was a prospective clinical trial which was designed to examine whether the timing in initial treatment prior to first psychosis had an effect on

outcomes (Johannessen 2001). The study was conducted in three first episode centres: two in Norway and one in Denmark. All patients were first episode patients and treatment protocols for psycho-social and pharmacological treatment was the same across all three sites. The TIPS project involved the establishment of an early detection system which consisted of early diagnosis teams which worked within the community and a comprehensive education programme about early psychosis. In this system emphasis is put on integrating the early detection system within the health services systems. After the initial period of four years a reduction in the duration of untreated early psychosis was detected from 114 weeks to 26 weeks, indicating the early detection system was working. There was also a significant difference in the way people came into treatment, with referrals coming from schools, families and patients themselves. A comparative study published in 2008 also reported that patients in the early detection areas of the TIPS study had lower durations of untreated psychosis than those in a comparable area which did not have early detection services (Melle et al. 2008). This suggests that the early detection efforts of the TIPS programme were having a positive effect on patients and final outcomes. TIPS has now evolved into a fully fledged early detection programme and involves educational outreach activities.

1997 Follow up conference on intervention for the first episode stage held in Stratford-upon-Avon, England

The UK National Early Psychosis conference focusing on first episode interventions in the first episode of psychosis was held in Stratford-upon-Avon, England, in June 1997. The participants at this conference were similar to those brought together in Melbourne in 1996, but also included other researchers from the UK. Importantly, Department of Health policymakers also spoke at this conference and were considered to be crucial to the change in early intervention mental health services for the first episode stage in the UK (Birchwood: Personal communication 2011). This conference also provided an opportunity for the formation of the inaugural International Advisory Board, which later became formalised as the International Early Psychosis Association (IEPA, see below).

1998 International Early Psychosis Association (IEPA) founded

At the first international early intervention conference in Melbourne in 1996, a strong feeling emerged among the conference attendees that an international association was needed to share information about research occurring in different parts of the world. After the Melbourne and Stratford-Upon-Avon conferences, the IEPA was founded in Victoria, Australia with the aim to improve knowledge, clinical care and service reform in early psychosis.

Early on, IEPA received unrestricted education grants from the Commonwealth of Australia and industry sponsors, including Janssen-Cilag and AstraZeneca. After 2003, the IEPA no longer needed external grants to support its work. The biennial conferences are

now supported by unrestricted educational grants from a variety of sponsors, some of which are summarised in this timeline.[7]

Currently, the IEPA is led by an international group of the leading researchers in the field, including Jean Addington from Canada, Peter Jones from the UK, Jeffrey Lieberman from the United States, and Alison Yung and Patrick McGorry from Australia. IEPA continues to offer clinicians and researchers a forum for disseminating findings and opportunities for networking among peers from around the world.

1999 Canada Mental Health Association early psychosis intervention project began (Canada)

In Canada, the Canadian Mental Health Association (CMHA) launched its early psychosis intervention project in 1999. Funded by the Population Health Fund of Health Canada, this initiative was designed to raise awareness of first episode interventions through the development of resource materials and to promote access to first episode services at three sites. The initiative had a particular focus on youth. The three participating sites were in the Calgary, Manitoba, and New Brunswick provinces. Beginning in 1997, Calgary's Early Psychosis Treatment & Prevention Program offered comprehensive outpatient services for those experiencing a first episode. In New Brunswick, the CMHA project provided an opportunity to reorganise existing clinical services to address early psychosis. Since Manitoba did not have any first episode intervention services, the CMHA project enabled stakeholders in the community to raise public awareness about the need for early intervention services (Lines 2000).

1999 First episode interventions referenced in National Service Framework (NSF) for Mental Health (England)

As a similar time to the developments occurring in Canada, England's National Service Framework (NSF) for mental health referenced first episode interventions (early intervention in the first episode stage) as a key component of providing mental health services and treatment. The NSF laid out strategies for improving prevention and first episode intervention services based in part on studies of Birmingham's Early Intervention Services. Professor Max Birchwood, who led the service and related research from its inception, had a significant role in writing the chapter on first episode interventions for the NSF and described the subsequent implementation of the framework over the next ten years as both a 'bottom-up' and 'top-down' effort (Birchwood: Personal communication 2011).

2000 Second international first episode intervention conference, held in New York

The IEPA convened the second formal international early intervention conference focused on the first episode stage (the first 'formal' international conference being the 1996 conference in Melbourne) in 2000 in New York. It was entitled *Future Possible*. Funding

[7] For a complete list of sponsorship from all conferences see http://iepa.org.au/about-us/sponsorship/. (Accessed, 21 October 2013)

for this conference came from a range of government and private sector sponsors including Janssen-Cilag, Pfizer, Lilly, Astra Zeneca, the New York State Office of Mental Health, and the National Alliance on Mental Illness. Similar to the first conference, the New York conference provided an opportunity for clinicians and researchers to network and share methods and findings.

2001 Mental Health Policy Implementation Guide prioritised the development of first episode intervention teams (England)

In 2001, a *Mental Health Policy Implementation Guide* was published by the Department of Health in England which prioritised the development of first episode intervention teams for first episodes of schizophrenia (Department of Health 2001). The guide states that effective first episode intervention services can: (1) reduce the stigma associated with psychosis and improve professional and lay awareness of the stigmas associated with psychosis; (2) reduce the amount of time people are untreated; (3) develop 'meaningful' engagement, provide evidence-based interventions and promote recovery; (4) increase stability in people's lives; provide a user-centered service; and (5) ensure transfer of care at the end of the service.

The guide recommends that first episode intervention services be provided for people aged 14–35 who have a first presentation of a psychotic illness or are somewhere during the first three years of psychotic illness. The guide establishes a series of care principles which should be followed in establishing first episode intervention services. These principles include providing services that are family oriented, culture, age and gender sensitive; enable meaningful and sustained engagement; provide treatment in an unrestrictive setting; provide separate, age-appropriate facilities for care; and emphasise normal social roles and symptom management. Many of these principles coincide with those established by earlier clinical service programs in the field, including the EPPIC and PACE programs in Australia and the Canadian first episode intervention services. However, the clinical evidence base on the effectiveness of these programmes was not available at the time the guidelines were developed. Rather, the key drivers of the Birmingham first episode intervention programme and the lobbying efforts of IRIS and RETHINK were critical to the development of England's national policy for interventions in the first episode stage.

2001 OPUS study of first episode stage reported first data (Denmark)

In 1999 a study in Denmark began to assess whether education and intensified collaborations between general practitioners, social services and other care providers would reduce the duration of untreated psychosis. In addition, the study sought to assess whether community treatment programs rather than treatment in community mental health hospitals would improve the course and outcomes for of young persons with schizophrenia (Jorgensen et al. 2000). The OPUS study consisted of 547 patients with a first episode of psychosis either receiving two years of assertive community treatment, family involvement and social skills training, or a standard course of treatment consisting of a contact with a community mental health centre. At the two-year follow up, patients who had received integrated treatment, significantly postponed or inhibited the onset of early psychosis, with

25 percent transitioning to a psychotic diagnosis compared with a 48 percent transition rate for patients in standard treatment (Petersen et al. 2008).

However, these results were not sustained at five-year follow up (Bertelsen 2008). After five years the effect of the integrated treatment as compared with the standard treatment had equalised, though a significantly smaller percentage of the experimental group of patients were living in supported housing and the treatment group had been hospitalised for fewer days. This may suggest that such integrated treatments need to be sustained in the long-term in order to have maximal effect (Bertelsen 2008). The OPUS study was funded by the Danish Ministry of Health and the Danish Medical Research Council.

2001 LEO study of early psychosis services for the first episode stage began (England)

In 2001, the Lambeth Early Onset (LEO) study began which was a randomised controlled trial of the effectiveness of specialised care for early psychosis (Power et al. 2007). The intervention was conducted by community mental health teams in a South London borough and consisted of assertive outreach with evidence-based biopsychosocial interventions such as low dose antipsychotic medication, cognitive behavioral therapy, family counselling and vocational training that were adapted for the patient. Patients in the standard care group received care delivered by community mental health teams, but these teams did not receive specialised training in dealing with early psychosis, though they were encouraged to follow available guidelines. Those in the specialised treatment group were less likely to relapse, had fewer hospital readmissions, and were less likely to drop out of the study. The study was funded by the Directorate of Health and Social Care London research and development organisation and management programme (part of the Brixton Early Psychosis Project).

2001 Several early psychosis programmes for the first episode stage launched in different countries, including Hong Kong, Singapore, and Switzerland

In 2001 many early psychosis programmes aimed at providing first episode intervention services launched in multiple countries all over the world. In Hong Kong, the Early Assessment Service for Young People with Psychosis (EASY) was launched in Hong Kong (Tang et al. 2010). This service was comprised of five specialised teams who worked with patients aged 15–25 presenting with symptoms of a first episode psychosis. The service was phase-specific, administering care based on the stage of the patient's psychosis. A cohort study looked at outcomes after three years and found that patients in the group which had received the first episode intervention had longer full-time employment, fewer days of hospitalization, less severe positive and negative symptoms of schizophrenia, and fewer suicides than those in the control group. However, both the intervention and the control groups had similar rates of relapse and durations of untreated psychosis (Hui et al. 2013).

The Early Psychosis Intervention Programme (EPIP) in Singapore began in 2001 and adopted a risk-reduction approach, seeking to reduce the duration of untreated psychosis through public education, networking with primary healthcare providers and providing special services for those in the prodromal phase of the illness (Verma et al. 2012).

Outcomes are now beginning to be reported for the service with a steady increase in the number of people enrolled in the service (Yin et al. 2011).

Finally, in 2001 the European Prediction of Psychosis Study (EPOS) also began. This four-country was funded by the European Fifth Framework Programme and was intended to provide a multi-centre, collaborative effort to collect data on persons at high risk of psychosis in different European countries and healthcare settings. The centres were located in six university departments in Germany (Cologne/Berlin), Finland (Turku), The Netherlands (Amsterdam) and the UK (Birmingham/Manchester). The study aimed to develop an improved, predictive clinical model of transition to first episode psychosis by drawing on patient data from the six centres across Europe and allowing for an 18-month follow up time. Two-hundred and forty-five patients enrolled in the study and findings were published in 2010. The combination of ultra high-risk and the cognitive disturbance recognition model (COGDIS) were found to have the best sensitivity in predicting the transition to psychosis (Ruhrman 2010).

2002 RETHINK established out of the National Schizophrenia Fellowship to fund work in early interventions services (England)

In 2002, RETHINK was launched out of the National Schizophrenia Fellowship (NSF). The NSF was an advocacy group formed in the early 1970s when several people who had individuals in their families with severe mental illness came together to try and change the mental health system and the way mental services operated in the UK. Currently, its mission is to help everyone affected by mental illness to have a better life. It provides practical support, services, advocacy, develops policy and provides education and training across England. First episode interventions are a central part of the services provide by RETHINK. In 2002, RETHINK launched the 'Reaching People Early' campaign. RETHINK and IRIS joined forces to lobby for the inclusion of first episode interventions in the national service framework for mental health and for a dedicated implementation programme to ensure it was implemented across the country.

2002 Third international conference for the first episode stage conference held in Copenhagen, Denmark

The third international conference focusing on interventions in the first episode stage was held in Copenhagen in 2002. Funding for the Copenhagen conference came from Eli Lilly, Pfizer, Bristol-Myers Squibb, and Janssen-Cilag. Abstracts and papers were published in a special issue of the *British Journal of Psychiatry* in 2005 (Volume 187, Issue 48).

Subsequent IEPA conferences have been held every two years, with funding coming from a range of pharmaceutical and non-pharmaceutical sponsors.[8]

[8] For a list of pharmaceutical sponsors for these conferences, see: http://iepa.org.au/about-us/sponsorship/. (Accessed, 21 October 2013)

2002 IRIS and WHO developed standards of care for early psychosis

Building on a meeting convened by IRIS to reach consensus on how to improve services for individuals with psychosis, first episode intervention supporters in England met with representatives from the World Health Organization, IRIS, and Rethink in 2002 at the launch of the National Institute for Mental Health in England (NIHME) to develop standards of care for early psychosis. The resulting Newcastle Early Psychosis Declaration focuses on supporting those with psychosis and their families to achieve positive outcomes and develop timely and effective interventions. Following the Newcastle Declaration, IRIS, NIMHE and Rethink worked together to promote its vision and values.

2002 First Episode Research Network (FERN) formed (England)

In 2002 the First Episode Research Network (FERN) was formed in England. FERN is a collection of National Health Service and social care organisations involved in the delivery of care to individuals with a first episode of psychosis. The network organisations have all agreed to compare data on the outcomes of the treatment that people are receiving in order to measure what constitutes best practice. The FERN group was run by Paul French and some of his colleagues in the South West and Gloucester regions of the UK. They wanted to compile a national database of outcomes of first episode intervention services, but they had trouble getting sufficient data of good quality. However, after the national evaluation project (entitled EDEN and described in further detail below) was funded by the NIHR, the work of FERN was gradually superseded and the effort died out.

2004 WHO and IEPA jointly issued a declaration on early intervention for early psychosis

In 2004, the Director of Mental Health for WHO formally released the early psychosis declaration at a national conference on intervention for the first episode stage in England. The IEPA collaborated on this consensus statement which was based on the Newcastle Declaration. In 2005, IEPA published international clinical practice guidelines for early psychosis.

2004 National Early Intervention Development Programme created to support early intervention policy development (England)

In England, policy and clinical practice followed quickly from the Newcastle Declaration and other events in the early 2000s. In 2004, the NIMHE (today known as the National Mental Health Development Unit (NMHDU)) created the National Early Intervention Development Programme (NEIDP) to support first episode intervention policy development. The overall aim of the programme was to: 1) provide a national vision, identity, leadership and vision for first episode intervention programmes; 2) carry out functions that are best conducted at a national level; 3) and encourage collaboration among the regions in England. Its activities were centered around three synergistic elements: policy, research and practice. It supported bottom-up policy development which would be more intensive and provide person-centred approaches to mental health service. In terms of research the efforts of the programme aimed at supporting the development of an evidence base for the effectiveness of interventions during the first episode stage,

including both cost effectiveness and controlled trials of EIP services on patient outcomes. Finally, the NEIDP informed practice and service development by providing information on standards of care and effectiveness of different models.

As has been referenced above, the work of IRIS and the model of first episode intervention services established in the West Midlands served as a key driver for the establishment of this programme. In addition, some important economic valuation work was also done to make the case for the health economics behind this kind of service (McCrone and Knapp 2007).

The programme provided development support for first episode intervention policy service implementation within the NHS through a series of measures. There were nationally coordinated and regionally delivered work programmes which aimed to integrate policy, research and practice development. A value-driven programme was established which placed the experiences and values of young service users and their families at the heart of the work programme, a philosophy based on the Newcastle Declaration. In order to establish credibility, the programme ensured that key programme 'leads' were fully engaged and 'visible' to the field. All 'leads' were involved with first episode interventions for at least twelve years which was thought to provide them with authenticity and local, regional, national and international respect. The leads were also able to provide advice to regional early intervention leads on local enquiries and could facilitate knowledge brokering activities and products like resource tools, factsheets, guidance, discussion papers and publications.

The programme was jointly funded by RETHINK and the Department of Health and the work of both RETHINK and IRIS in making the case for its establishment was crucial. Dr David Shiers, the Birmingham general practitioner who formed IRIS and Jo Smith, were the joint leads for the programme at a national level. They, and other key advocates, played a role in mediating between the local implementation and the top-down coordination across the country. The programme was also influenced by the Birmingham Early Intervention Service (focused on services provided in the first episode stage).

The programme was discontinued in 2010 because the funding for initial rollout came to an end. However, first episode intervention services are now established throughout England as a standard part of mental health care delivered by NHS trusts. A final conference was held in February 2010 to discuss what the programme had achieved and critical next steps. The conference was titled *Early Intervention in England: The Story So Far*.

2006 National EDEN project findings of first episode stage reported (England)

The National EDEN project (A National Evaluation of Early Intervention for Psychosis Services) was an evaluation of first episode intervention service teams after the government introduced a new programme of these services for people aged 14–35. The evaluation would focus on key aspects of service delivery which maximise effectiveness of services, identification of service delivery configurations which lead to success, and provide information on the relationship between service configurations, fidelity to national early intervention guidelines and key, pre-defined patient outcomes. Many of the individuals

(Birchwood, Macmillan) who were involved in the initial first episode intervention services in Birmingham (UK) and who have been involved in advocacy for first episode intervention services in the UK, are the PIs on this evaluation project. The project was funded by the NIHR and completed its evaluation and reported on key lessons in 2007 (Birchwood et al. 2006).

The EDEN project is now being followed up by SUPEREDEN (Sustaining Positive Engagement and Recovery), another NIHR programme grant that includes a series of three projects focusing on maximising the impact, cost-effectiveness and user experiences of first episode intervention services, exploring qualitative assessments of the programme, and improving social recovery in young people through a randomised controlled. SUPEREDEN enrolled patients until December 2011 for the user experience parts of the study around cost effectiveness and impact (Study 1) and qualitative investigation of care, staff and user experience (Study 2). Study 3 will finish recruiting in 2013. The study is a randomised controlled trial aimed at improving social recovery in young people with non-affective psychosis.

2007 Omega-3 fatty acid intervention trial of prodromal stage published (Austria)

In 2007 a group of researchers published data from a randomised, double-blind, placebo controlled trial of the effect of long-chain, omega-3 polyunsaturated fatty acids on reducing the rate of progression to first episode psychotic disorder in adolescents and young adults in Austria (Amminger et al. 2010). The study was developed by the clinical research group at EPPIC, but carried out in Vienna. The group used insights from other research which suggested that dysfunctional fatty acid metabolism could play a role in the etiology of schizophrenia. This led them to hypothesis that long-chain, omega-3 fatty acids may have a beneficial effect on transition to psychosis. The presence of attenuated psychosis symptoms and transient psychosis in the patient group was determined using a semi-structured interview and applying Positive and Negative Syndrome Scale (PANSS) cutoff scores for severity of symptoms and frequency and duration criteria proposed by Alison Yung and colleagues at the PACE clinic. Among those who completed the, full twelve-week intervention, 5 percent in the omega-3 group and 28 percent of those in the placebo group converted to psychosis. The risk of transition to psychosis was significantly less for the treatment group. The trial holds promise for this type of intervention, but needs to be replicated with a larger sample and have at least six-month follow up for all patients (Marshall and Rathbone 2011). The initial study was funded by the Stanley Foundation and they are also currently funding a replication study.

2007 Early Intervention in Psychiatry journal launched by IEPA

In 2007, the IEPA launched the journal Early Intervention in Psychiatry that focuses on early diagnosis and intervention in the field of psychiatry. It provides a common forum for researchers and clinicians with an interest in the early phases of a wide range of disorders to share ideas, experience and data. The editor-in-chief is Patrick McGorry.

2007 Early Detection and Intervention Evaluation Trial for prodromal stage published findings (England)

In 2007 a research group from the University of Manchester and the Bolton, Salford and Trafford Mental Health Trust published three-year follow-up data from their randomised controlled trial of cognitive therapy (CT) as an intervention to prevent psychosis (Morrison et al 2007). The study compared CT with monthly monitoring in 58 patients who met criteria for being at ultra high risk of psychosis Morrison et al. 2004). The criteria used to make the determination of being at high risk were the PACE criteria (discussed above). The study found that an intensive six-month period of treatment through cognitive therapy was effective in reducing the likelihood of being prescribed anti-psychotic medication in a help-seeking, high-risk group, but was not effective in reducing likelihood of transition to psychosis. However, if only using the PANSS criteria for transition to psychosis and after controlling for beliefs that are targeted during therapy, CT did significantly reduce the risk of transition to psychosis. This study was funded by the North West National Health Service R&D Executive and the Stanley Medical Research Institute.

2009 RAISE research project of first episode intervention services began (United States)

The Recovery After an Initial Schizophrenia Episode (RAISE) is a research project supported by the National Institute of Mental Health. The goal of RAISE is to develop and test interventions in the early stages of schizophrenia. RAISE is being conducted by two teams. The RAISE Early Treatment Program is a research project at 35 community-based clinics in 21 states. The clinics will be randomly assigned to administer either the intervention services or usual community treatment programme services. Programme participants at treatment clinics will receive psychopharmacological treatment, family psychoeducation, supported employment, individual resiliency training, and individualised case management. The RAISE Connection Program is being conducted at community clinics in Maryland and New York.

2010 National Early Intervention Development Programme concluded with final conference in Birmingham (England)

In 2010 the National Early Intervention Development Programme came to an end and its conclusion was marked by a final conference held in Birmingham. The conference included discussions about progress to date and experiences of service users, as well as regional workshops and action planning for next steps. The end of the programme does not mark the end of the effort, though, as the main purpose of the programme was to inform policy, research and practice. First episode intervention services are now in place across the country and working to fulfill local community needs in the most appropriate ways. Therefore, although the development programme has ended, the relationships and practices established still exist.

2012 Current state of affairs

Currently first episode intervention programmes are at different stages of implementation depending on the country. Among the countries that are the focus of this case study, the

UK, intervention programmes for the first episode stage are embedded in the majority of mental health services across the country. Though the exact nature of programmes and services offered may vary by region, the core principles of interventions after the first episode are embedded in practice, recommended by national clinical practice guidelines (see below), and in the national mental health strategy. In the US, intervention services and programmes for the first episode stage are fewer in number and vary in their delivery. The more prominent programmes include the Portland Identification and Early Recognition (PIER) service (Portland, Maine), the PRIME center (Yale University, New Haven, Connecticut), the Recognition and Prevention Programme (Feinstein Institute for Medical Research, New York), the Therapeutic Early Intervention Services programme in Pittsburgh, and the Early Assessment and Support Team (EAST) in Salem, Oregon. One reason for this variation in the nature of services may be that the nature of the US healthcare system makes it difficult to establish a common set of services and programmes. Intervention services for the first episode stage in Canada are widespread throughout the country and embedded at local levels, though like the US the formal guidelines in Canada do not explicitly recommend tailored first episode intervention treatment approaches after a first episode of psychosis.

No country explicitly recommends prodromal interventions, though as can be seen from the studies and initiatives summarised above there are many trials and efforts underway to try and better understand how to classify patients as being at ultra high risk of transitioning to psychosis, and what mix of interventions is most appropriate to prevent this. Recently, Australia was considering introducing youth mental health reforms which aimed to address some of these diagnostic problems. However, amid national and international outcry, these reforms were eventually dropped. In addition, changes were considered in the US related to the development of DSM-V. At the beginning of the DSM-V revision process, it was thought that the APA might include a Risk Syndrome for risk of psychosis (called 'attenuated psychosis symptoms') to enable earlier diagnosis, and hence either first episode or prodromal interventions to be more easily administered. However, this was dropped in the face of opposition from many in the field who argued that this risk syndrome would lead to many 'false positive' diagnoses, as well as unnecessary stigmatisation and discrimination, and, moreover, the evidence base for it was not fully developed to merit inclusion.

The adoption and evolution of early intervention in clinical guidelines

In the US, the American Psychiatric Association (APA) 2004 practice guidelines for the treatment of schizophrenia note that it is important to treat as early as possible in the initial episode of psychosis with close observation and documentation of signs and symptoms so progression of psychosis can be tracked. Prodromal interventions as a treatment approach is mentioned only briefly in a section on psychosocial treatments which have a very limited evidence base. Citing randomised control trials of treatment during the prodromal stage, the guidelines indicate that intervention during the prodromal stage can be effective in lowering the likelihood of relapse (American Psychiatric Association 2006). However, the guidelines note that more studies are needed before treatment recommendations are warranted. The 2009 Guideline Watch for Schizophrenia provides an update on studies since the release of the 2004 practice guidelines. In this

update, intervening early and intervention as a treatment approach for either the prodromal or first episode stages are not mentioned at all (Dixon et al 2009). In 2010, researchers on the Schizophrenia Patient Outcomes Research Team (PORT) updated their schizophrenia treatment recommendations to propose the use of antipsychotic medications other than clozapine/olanzapine during the first episode stage (Kreyenbuhl et al. 2010; Buchanan et al 2010). However the updated PORT recommendations did not suggest psychosocial interventions during the first episode stage because of the limitations of the evidence base (Dixon et al 2010).

In England, the 2002 National Institute for Health and Clinical Excellence (NICE) guidelines on schizophrenia noted the emergence of comprehensive treatments using an intervention approach which was initiated earlier in the treatment stages, but did not find sufficient evidence to recommend an specific intervention model at either the first episode or prodromal stage (NICE 2002). The guidelines describe 'early intervention' as identification and therapy for those in the prodromal stage and pharmacological and psychosocial intervention for those in the first episode stage, both delivered by a specialised treatment team. The 2009 update to the NICE guidelines on schizophrenia acknowledge that studies have begun to show the benefits of intervention in both the prodromal and first episode stages. Citing the PACE study of pharmacotherapy and cognitive behavior therapy during the prodromal stage, the guidelines recognise that first episode or prodromal interventions are an emerging area that warrants continued attention. Importantly, the guidelines state that 'Providing treatment for people in a possible prodromal stage of schizophrenia is an interesting but potentially controversial area, which at present is outside the scope of this guideline.' As such, the current NICE guidelines recommend providing first episode intervention services that include the full range of pharmacological, psychological, social, occupational, and educational interventions during the first episode stage but not during the prodromal stage (NICE 2009).

In Canada, the Canadian researchers responsible for the development and implementation of the first episode intervention clinical programs were involved in writing the clinical guidelines. The 2005 Treatment of Schizophrenia clinical practice guidelines describe early psychosis treatment services in the service delivery section. The guidelines note that intervention services for those in the first episode stage are important because of the trajectory of psychosis after the first episode, the link between phase specific treatment and outcomes, and the increased likelihood of negative outcomes when treatment is delayed. The guidelines acknowledge that the evidence of the relationship between early psychosis services and reducing the duration of untreated psychosis and improving treatment outcomes is still scant. The guidelines include a discussion of the prodromal stage as a special issue noting that there is only preliminary evidence from the PACE and PRIME studies of the effectiveness of antipsychotics and cognitive behavioral therapy during this stage (Canadian Psychiatric Association 1999).

In 2005, the International Early Psychosis Association published interventional clinical practice guidelines for early psychosis (International Early Psychosis Association Writing Group 2005). For the premorbid and prodromal stages, the guidelines define criteria for having an 'at-risk mental state' and standards of care for those found to be at-risk. The guidelines note that antipsychotic medications are warranted during these stages only when the patient is diagnosed with a full threshold psychotic disorder. For the first episode

stage, the guidelines detail standards of care for access, location of treatment, and initial management using anti-psychotic medications and cognitive-behavioral therapy. Other countries, including Australia and New Zealand, have also developed early psychosis clinical practice guidelines.

In conclusion, the main differences in national guidelines are between the UK and the US/Canada. The UK NICE guidelines recommend intervention after the first episode, while the APA and Canadian guidelines say that tailored interventions at the first episode stage can be beneficial, but they do not go so far as to recommend it.

4.5 Observations on the development of early intervention

There have been many diverse and varied events which characterise the research and development of intervention services for the prodromal and first episode stages of schizophrenia. As pointed out at the beginning of the case study, much of the research done in this area is tied to clinical service delivery. In the absence of an overarching national research and development strategy in the early stages, many of the key events and initiatives were driven by particular researchers and occurred in regions in which those researchers worked. For example, the work of Patrick McGorry and Alison Yung at the EPPIC centre and PACE clinic in Australia appears to be one central driving force for the field, but began locally. The intervention programs and services in Australia for both the prodromal and first episode stages not only established a foundational evidence base for these kind of intervention services, but also brought many researchers together in the early stages to form an international network which then began to establish similar programmes and services in their local areas. This grassroots, clinically driven first episode and prodromal intervention research is found in other countries as well, such as England, Canada, Australia and others.

Despite locally strong trends and initiatives in different countries, out of our three case study countries, only England has evidence of a national research and clinical delivery strategy for intervention in the first episode stage. In England, there has been considerable policy and advocacy activity at a national level which has been particularly strong in recent years. This began in 1999 when first episode interventions were referenced in the National Service Framework for mental health. Though much of this advocacy started locally in the West Midlands, it spread nationally through coordinated action and grassroots campaigns. In 2001, the Mental Health Policy Implementation Guide prioritised development of first episode intervention teams. In 2004, the National Institute of Mental Health for England created a National Early Intervention Development Plan.

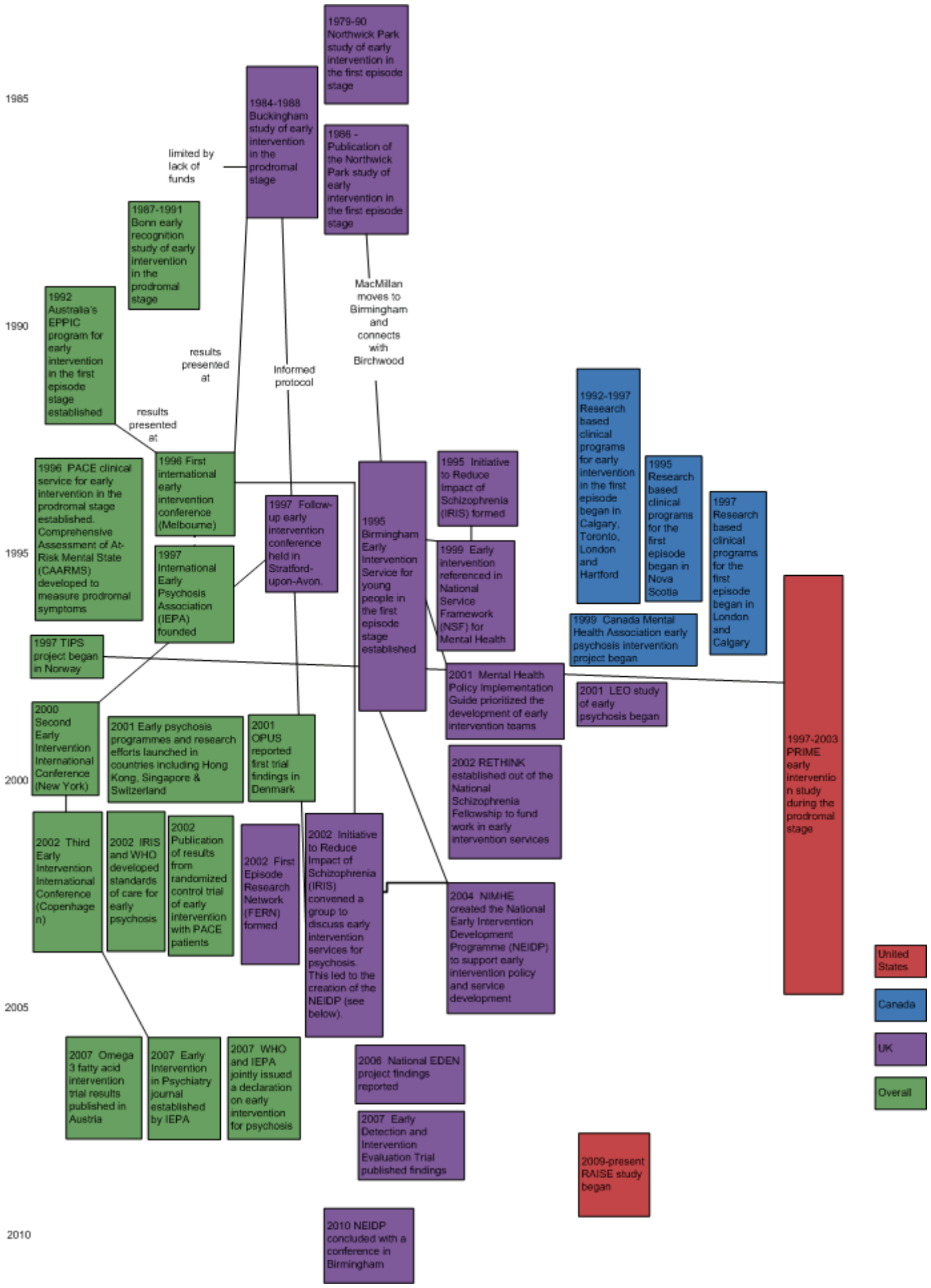
There has been much more limited national policy activity in the US and Canada. In the US, the PRIME study and prodromal research has been confined to a few local efforts and individuals. Only recently, the National Institute of Mental Health funded RAISE, a national, multi-centre study to develop and test interventions in the early stages of schizophrenia. Canadian research in first episode interventions has also been locally driven within individual provinces and tied to clinical service delivery. Even in Australia, national policy has only recently prioritised investment in early intervention services and research, for both first episode and prodromal stages, though this has raised some controversy, especially in regard to prodromal intervention services. While complex, the debate has

largely centered around the perception that there is a weak evidence base for intervention in the prodromal stage because it is so difficult to establish prodromal symptoms, themselves.

Overall, the lack of national policy and advocacy activity has meant there are differences across countries in clinical practice guidelines for first episode and prodromal interventions in schizophrenia. In England, the NICE guidelines recommend tailored interventions for the first episode stage. The US and Canadian clinical practice guidelines note the importance of early intervention for the first episode stage but do not explicitly recommend early intervention as a treatment approach. Without clear and strong recommendations in clinical practice guidelines, the adoption of first episode and prodromal interventions will continue to be challenging.

There are other challenges to the widespread adoption of early intervention services. As has been evident throughout this case study, there is a lack of clarity about the psychotic stage at which 'early intervention' services are directed. The term 'early intervention' can be used to refer to both the prodromal stage and the first episode stage with considerably different service and research implications. Intervention in the prodromal stage raises important questions about the clinical definition of this phase and how it is diagnosed and treated. In addition, research on the prodromal stage is limited to a handful of clinical trials. Many agree that before prodromal intervention services can be fully implemented at this stage, there must be more trials and research done to establish effectiveness and efficacy. Moreover, even if this research were to be done, there would still be barriers before prodromal intervention is adopted into practice. For example, the clinical diagnostic criteria which would be used to establish when someone is in the prodromal stage is a major question. For some in the field, there are also still lingering questions about the clinical diagnosis of the first psychotic episode. Further, even if clinical diagnostic criteria are established, there would still be barriers to implementation in healthcare systems like the US, where access to psychosocial services, in particular, are limited and highly variable.

Overall, research on first episode and prodromal interventions for schizophrenia in the three focus countries has been largely characterised by local clinical programmes and studies, although national funding agencies have funded some work. The researchers and clinicians involved in these efforts have collaborated through international conferences and organisations to establish guiding principles for intervention services and care in the first episode stage. However, at the national level only in England has there been policy and advocacy activity to encourage widespread adoption of intervention in the first episode stage. The evidence base for interventions at both the prodromal and first episode stages is not strong. As a result, the clinical practice guidelines across the three countries vary, with the NICE guidelines recommending intervention in the first episode stage and the APA and Canadian guidelines noting the importance of intervention for early psychosis but not explicitly recommending a tailored treatment approach. With none of the guidelines recommending intervention for the prodromal stage, the evidence base for this stage needs further development.


1985
1990
1995
2000
2005
2010
1979-90 Northwick Park study of early intervention in the first episode stage
1984-1988 Buckingham study of early intervention in the prodromal stage
limited by lack of funds
1986 - Publication of the Northwick Park study of early intervention in the first episode stage
1987-1991 Bonn early recognition study of early intervention in the prodromal stage
MacMillan moves to Birmingham and connects with Birchwood
1992 Australia's EPPIC program for early intervention in the first episode stage established
results presented at
Informed protocol
results presented at
1992-1997 Research based clinical programs for early intervention in the first episode began in Calgary, Toronto, London and Hartford
1995 Research based clinical programs for the first episode began in Nova Scotia
1997 Research based clinical programs for the first episode began in London and Calgary
1996 PACE clinical service for early intervention in the prodromal stage established. Comprehensive Assessment of At-Risk Mental State (CAARMS) developed to measure prodromal symptoms
1996 First international early intervention conference (Melbourne)
1997 Follow-up early intervention conference held in Stratford-upon-Avon.
1997 International Early Psychosis Association (IEPA) founded
1995 Birmingham Early Intervention Service for young people in the first episode stage established
1995 Initiative to Reduce Impact of Schizophrenia (IRIS) formed
1999 Early intervention referenced in National Service Framework (NSF) for Mental Health
1999 Canada Mental Health Association early psychosis intervention project began
1997 TIPS project began in Norway
2001 Mental Health Policy Implementation Guide prioritized the development of early intervention teams
2001 LEO study of early psychosis began
1997-2003 PRIME early intervention study during the prodromal stage
2000 Second Early Intervention International Conference (New York)
2001 Early psychosis programmes and research efforts launched in countries including Hong Kong, Singapore & Switzerland
2001 OPUS reported first trial findings in Denmark
2002 RETHINK established out of the National Schizophrenia Fellowship to fund work in early intervention services
2002 Third Early Intervention International Conference (Copenhagen)
2002 IRIS and WHO developed standards of care for early psychosis
2002 Publication of results from randomized control trial of early intervention with PACE patients
2002 First Episode Research Network (FERN) formed
2002 Initiative to Reduce Impact of Schizophrenia (IRIS) convened a group to discuss early intervention services for psychosis. This led to the creation of the NEIDP (see below).
2004 NIMHE created the National Early Intervention Development Programme (NEIDP) to support early intervention policy and service development
2007 Omega 3 fatty acid intervention trial results published in Austria
2007 Early Intervention in Psychiatry journal established by IEPA
2007 WHO and IEPA jointly issued a declaration on early intervention for psychosis
2006 National EDEN project findings reported
2007 Early Detection and Intervention Evaluation Trial published findings
2009-present RAISE study began
2010 NEIDP concluded with a conference in Birmingham
United States
Canada
UK
Overall

4.6 References

American Psychiatric Association (2006). *Practice Guidelines for the Treatment of Psychiatric Disorders: Compendium 2006*. Arlington, VA: American Psychiatric Association.

Amminger, G. P., et al. (2010). 'Long-chain ϙ-3 Fatty Acids for Indicated Prevention of Psychotic Disorders.' *Archives of General Psychiatry,* 67(2), 146–154.

Bertelsen, M., Jeppesen, P., Petersen, L., Thorup, A., Øhlenschlaeger, J., le Quach, P., Christensen, T. Ø., Krarup, G., Jørgensen, P. and Nordentoft, M. (2008). 'Five-year follow-up of a randomized multicenter trial of intensive early intervention vs standard treatment for patients with a first episode of psychotic illness: the OPUS trial.' *Archives of General Psychiatry*, 65(7), 762–71.

Birchwood, M., Todd, P. and Jackson, C. (1998). 'Early intervention in psychosis: the critical-period hypothesis.' *International Clinical Psychopharmacology*, 13(S1), S31-S40.

Birchwood, M., and MacMillan, J. F. (1993). 'Early intervention in schizophrenia.' *Australian and New Zealand Journal of Psychiatry*, 27, 374-378.

Birchwood, M. et al., (2006). 'EDEN: Evaluating the development and impact of Early Intervention Services (EISs) in the West Midlands.' As of 21 October 2013: www.netscc.ac.uk/hsdr/files/project/SDO_RS_08-1304-042_V01.pdf

Birchwood, M. (2011). *Personal communication with Molly Morgan Jones and Dana Schultz.* Interview: Birmingham, UK.

Buchanan, R. W., Kreyenbuhl, J., Kelly, D. L., et al. (2010). 'The 2009 Schizophrenia Patient Outcomes Research Team (PORT) psychopharmacological treatment recommendations and summary statements.' *Schizophrenia Bulletin,* 36(1), 71–93.

Canadian Psychiatric Association (1999). 'Canadian clinical practice guidelines for the treatment of schizophrenia.' *Canadian Journal of Psychiatry*, 43 (Suppl. 2), 25s–40s.

Chen, E. Y. H. (1999). 'Early intervention in schizophrenia patients— rationale for its implementation and practice.' *Hong Kong Medical Journal,* 5(1), 57–62.

de Koning, M. B., Bloemen, O. J. N., van Amelsvoort, T. A. M. J., Becker, H. E., Nieman, D. H., van der Gaag, M., Linszen, D. H. (2009). 'Early intervention in patients at ultra high risk of psychosis: benefits and risks.' *Acta Psychiatrica Scandinavica,* 119, 426-442.

Department of Health (2001) Mental Health policy implementation guide. London. Stationery Office: London.

Dixon, L., Perkins, M. D., Calmes C. C. (2009). *Guideline Watch (September 2009): practice guidelines for the treatment of patients with schizophrenia*. Arlington, VA: American Psychiatric Association.

Dixon, L. B., F. Dickerson, et al. (2010). The 2009 Schizophrenia Patient Outcomes Research Team PORT psychosocial treatment recommendations and summary statements. *Schizophrenia Bulletin*, 36(1), 48–70.

Fadden, G. and Heelis, R. (2011) 'The Meriden West Midlands Family Programme: Lessons Learned Over Ten Years.' *Journal of Mental Health*, 20(1), 79–88.

Falloon, I. R. (2000) 'General practice recruitment for people at risk of schizophrenia: the Buckingham experience.' *Australian and New Zealand Journal of Psychiatry* 34(Suppl.), S131–S136; discussion S140–S144.

Falloon, I. R. H., Kydd, R. R., Coverdale, J. H., Tannis, M. L. (1996). 'Early detection and intervention for initial episodes of schizophrenia.' *Schizophrenia Bulletin*, 22, 271–282.

Falloon, I.R.H., Coverdale, J.H., Laidlaw, T.M., Merry, S., Kydd, R.R., Morosini, P. (1998). 'Early intervention for schizophrenic disorders: Implementing optimal treatment strategies in routine clinical services.' *British Journal of Psychiatry*, 33, 33–38.

Hui, C. L-M, Tang, J. Y-M, Leung, C-M, Wong, G. H-Y, Chang W-C, Chan, S. K-W, Lee, E. H-M and Chen, E. Y-H (2013). 'A 3-year retrospective cohort study of predictors of relapse in first-episode psychosis in Hong Kong.' *Australian and New Zealand Journal of Psychiatry*. April 23, 2013.

International Early Psychosis Association Writing Group (2005). 'International clinical practice guidelines for early psychosis.' *British Journal of Psychiatry*, Suppl. 48, s120–s124.

Johannessen J. O. (1998). 'Early intervention and prevention in schizophrenia-experiences from a study in Stavanger, Norway.' *Seishin Shinkeigaku Zasshi*, 100, 511–22.

Johannessen, J. (2001). 'Early detection strategies for untreated first-episode psychosis.' *Schizophrenia Research*, 51, 39–46.

Johnstone, E. C., Crow, T. J., Johnson, A. L., MacMillan, J. F. (1986). 'The Northwick Park Study of first episodes of schizophrenia.' *British Journal of Psychiatry,* 148, 115–120.

Jorgensen, P., Nordentoft, M., Abel, M. B., et al., (2000). 'Early detection and assertive community treatment of young psychotics: the Opus Study rationale and design of the trial.' *Social Psychiatry and Psychiatric Epidemiology*, 35, 283–287.

Klosterkotter T. J., Schultze-Lutter F., Gross G., Huber G., Steimeyer, E. M. (1997). 'Early self-experienced neuropsychological deficits and subsequent schizophrenic diseases: an 8-year average follow-up prospective study.' *Acta Psychiatrica Scandinavica*, 5, 396–404.

Kreyenbuhl, J., Buchanan, R. W., et al. (2010). 'The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2009.' *Schizophrenia Bulletin,* 36(1), 94–103.

Larsen, T. K., Friis, S., Haahr, U., et al. (2001) 'Early detection and intervention in first-episode schizophrenia: a critical review. *Acta Psychiatrica Scandinavica*, 103, 323–334.

Lines, E. (2000). *Canadian Early Psychosis Initiatives*. Toronto: Canadian Mental Health Association.

McCrone and Knapp (2007). 'Economic valuation of early intervention services. *British Journal of Psychiatry*, 191, s19-s22.

McGlashan, T. (1998). 'Early detection and intervention of schizophrenia: rationale and research.' *British Journal of Psychiatry*, 172(S33), 3–6.

McGlashan, T. (2003). 'Progress, issues, and implications of prodromal research: an inside view.' *Schizophrenia Bulletin*, 29 (4), 851–858.

McGlashan, T. (2011). *Personal communication with Professor Tom McGlashan*: *telephone interview with Molly Morgan Jones*. Cambridge, UK.

McGorry, P., Edwards, J., Mihalopoulos, C., Harrigan, S. M. and Jackson, H. J. (1996). 'EPPIC: An Evolving System of Early Detection and Optimal Management.' *Schizophrenia Bulletin*, 22 (2), 305–326.

McGorry, P. (1998). 'Preventive strategies in early psychosis: verging on reality.' *The British Journal of Psychiatry*. 172(33), 1–2.

McGorry, P. D., Yung, A. R., Phillips, L. J., Yuen, H. P., Francey, S., Cosgrave, E. M., Germano, D., Bravin, J., McDonald, T., Blair, A., Adlard, S., Jackson, H. (2002). 'Randomized Controlled Trial of Interventions Designed to Reduce the Risk of Progression to First-Episode Psychosis in a Clinical Sample With Subthreshold Symptoms.' *Archives of General Psychiatry*, 59, 921–928.

McGorry, P. (2012). *Personal email communication with Patrick McGorry and Molly Morgan Jones.* Cambridge UK.

Malla, A. K., Norman, R. M. G., Voruganti, L. P. (1999). 'Improving outcome in schizophrenia: the case for early intervention.' *Canadian Medical Association Journal*, 160(6), 843–846.

Marshall, M. and Rathbone, J. (2010). 'Early intervention for psychosis.' *Cochrane Database of Systematic Reviews 2006*, 4, Art. No.: CD004718.

Marshall M. and Rathbone J. (2011) Early intervention for psychosis. *Cochrane Database of Systematic Reviews* 2011, 6, Art. No.: CD004718.

Melle I., Larsen T. K., Haahr U., et al. (2008). 'Can the deficit syndrome be altered in first episode schizophrenia? Two year effects of reducing the duration of untreated psychosis.' *Archives of General Psychiatry* 65, 634–640.

Miller, R., Mason, S. (1999). 'Phase-specific psychosical interventions for first-episode schizophrenia.' *Bulletin of the Menninger Clinic*, 63, 499-519.

Miller, T. J., Zipursky, R. B., Perkins, D., Addington, J., Woods, S. W., Hawkins, K. A., et al. (2003). 'The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally symptomatic for psychosis. II. Baseline characteristics of the "prodromal" sample.' *Schizophrenia Research*, 61, 19–30.

Morrison, A. P., French, P., Walford, L., et al. (2004). 'Cognitive therapy for the prevention of psychosis in people at ultra-high risk.' *British Journal of Psychiatry*, 185, 291–297.

Morrison, A. P., French, P., Parker, S,. et al. (2007) 'Three-year follow-up of a randomized controlled trial of cognitive therapy for the prevention of psychosis in people at ultrahigh risk.' *Schizophrenia Bulletin*, 33, 682-87.

NICE (National Institute for Health and Clinical Excellence) (2002). *Schizophrenia*. London: NICE.

NICE (National Institute for Health and Clinical Excellence) (2009). *Schizophrenia*. London: NICE.

Petersen L,. Thorup A., Øqhlenschlaeger J., Christensen T. Ø., Jeppesen P., Krarup G., Jørrgensen P., Mortensen E. L., Nordentoft M. (2008). 'Predictors of remission and recovery in a first-episode schizophrenia spectrum disorder sample: 2-year follow-up of the OPUS trial.' *Canadian Journal of Psychiatry*, 53(10), 660–70.

Pollitt, A., Diepeveen, S., Guthrie, S., Morgan Jones, M., Ní Chonaill, S., Olmsted, S., et al., (2013). *Mental Health Retrosight: Understanding the returns from research (case studies)*. Cambridge, UK: RAND Europe.

Power, P., et al. (2007). 'The Lambeth Early Onset Crisis Assessment Team Study: general practitioner education and access to an early detection team in first-episode psychosis.' *The British Journal of Psychiatry*, Suppl., s133-s139.

Ruhrman, S., Schultze-Lutter, F., Salokangas, R. K. R., et al. (2010). 'Prediction of psychosis in adolescents and young adults at high risk.' *Archives of General Psychiatry*, 67(3), 241-51.

Tang J. Y., Wong G. H., Hui C. L., Lam M. M., Chiu C. P., Chan S. K., Chung D. W., Tso S., Chan K. P., Yip K. C., Hung S. F., Chen E. Y. (2010). 'Early intervention for psychosis in Hong Kong: the EASY programme.' *Early Intervention in Psychiatry*, 4(3), 214–9.

Verma, S. et al., (2012). 'The Singapore Early Psychosis Intervention Programme (EPIP): A programme evaluation.' *Asian Journal of Psychiatry*, 5(1), 63–67.

Wyatt, R. J. and Henter, I. (2001). 'Rationale for the study of early intervention.' *Schizophrenia Research*, 51, 69–76.

Yin, P. L. et al. (2011). 'Outcomes of the Early Psychosis Intervention Programme (EPIP),' S*ingapore Family Physician*, 37(4), 48–51.

Yung, Alison R., Hok Pan Yuen, McGorry, P. D., Phillips, L. J., Kelly, D., Dell'Olio, M., Francey, S. M., Cosgrave, E. M., Killackey, E., Stanford, C., Godfrey, K. and Buckby, J. (2005). 'Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States.' *Australian and New Zealand Journal of Psychiatry*, 39, 964–971.

CHAPTER 5 Clozapine

5.1 Summary

Clozapine, a tricyclic drug developed in 1959 by Wander AG, came to prominence because of its atypical pharmacological properties, unique profile of therapeutic effects and serious adverse effects. Despite great clinical promise, clozapine's market launch was plagued with potentially life-threatening treatment-emergent effects, and in the US, prohibitively high costs. Although clozapine's superior effectiveness in the management of treatment-resistant schizophrenia and suicidal behavior among patients with schizophrenia has been recognised by all major clinical practice guidelines, the drug has yet to be broadly adopted for these indications.

In the 1960s and early 1970s, widespread scepticism existed over the drug's potential antipsychotic efficacy, because it was not associated with extrapyramidal symptoms (movement disorders, such as acute dystonic reactions or akathisia). After empirical studies proved the sceptics wrong, clozapine finally reached major European markets in the mid-1970s. At around the same time, Sandoz, the company now responsible for its research and development (R&D), established an outpost in the US under the helm of Gil Honigfeld.

Although dangerous cases of orthostatic hypotension and tachycardia observed in 1974 among healthy Phase II trial participants in the US were successfully dealt with, the deaths in 1975 of nine of eighteen Finnish inpatients who had developed serious hematological disorders soon after starting clozapine were far more consequential. The drug was removed from many European countries. In the US, although clozapine remained available through a compassionate need programme, all R&D efforts were suspended. Overwhelmingly positive feedback from patients/families and clinicians, the passion and persistence of Gil Honigfeld and academic researchers, and the active collaboration of the US Food and Drug Administration (FDA) eventually led to its approval in 1989 for use in treatment-resistant patients and with the proviso that the company devises a system to minimise hematological risks. To comply with the regulator's terms, Sandoz marketed its branded product (Clozaril) as a highly controversial and expensive bundled product: the Clozaril Patient Management System. By 1991, in the wake of a class action antitrust law suit, Clozaril was unbundled in the US, and the following year, two years before its period of exclusivity had ended, Sandoz significantly scaled back Clozaril marketing resources.

In 1995, acting on observational evidence of clozapine's anti-suicidal benefits, Sandoz requested US FDA approval for an anti-suicidal indication. Rejection of the request (on the grounds that randomised evidence was lacking) led the company, now called Novartis, to sponsor the InterSePT study, a large international randomised controlled trial.

InterSePT's finding of clozapine's superiority over other second-generation antipsychotics (SGA) in the management of suicidal behavior paved the way for US FDA approval of the drug's second unique indication in 2002. Shortly thereafter, however, Novartis' CEO halted promotional efforts related to the anti-suicidal indication.

By 2003, growing evidence that clozapine and other SGAs were associated with metabolic side effects led the US FDA to issue a warning on the increased risk of treatment-emergent hyperglycemia and related adverse events associated with SGA use.

Despite clozapine's risks however, recent evidence has not only confirmed its superiority for treatment-resistant psychosis but has also shown that the drug is associated with substantially lower mortality than all other antipsychotics.

5.2 Focus of case study

This case study focuses on barriers and facilitators to the development and adoption of clozapine, the prototype *atypical* (second-generation) antipsychotic agent. Although still unrivalled in its effectiveness, clozapine is associated with multiple side effects, some of which are serious and life-threatening.

5.3 Glossary

Agranulocytosis: Condition involving a severe and dangerous form of leukopenia (abnormally low white blood cell count).

Antipsychotic drugs: Also referred to as neuroleptics, medications used to control psychotic symptoms. Two classes of antipsychotic drugs exist: first-generation (or conventional) and second-generation (or atypical). This classification is based on their mechanism of action. However, while all first-generation antipsychotics were developed between the 1950s and the 1980s, all second-generation antipsychotics with the exception of clozapine were developed since the 1990s.

Apomorphine Antagonism: As a result of the competition for dopaminergic receptors between apomorphine, a morphine decomposition product, and typical antipsychotics, the reduction of antipsychotic effect in the presence of apomorphine.

Apomorphine Gnawing Test: The induction of chewing behavior in mice associated with administration of apomorphine.

Atypicality: Absence of extrapyramidal side effects.

Cataleptic: Characterised by lack of response to external stimuli and by muscular rigidity.

Extrapyramidal Symptoms: Involuntary movements reflecting abnormal extrapyramidal function that may be observed with antipsychotic drug treatment. These include acute dystonic reactions, parkinsonism and akathisia.

Hematological: Related to blood and blood-producing organs.

Hyperglycemia: Presence of excessive amount of glucose in the blood plasma.

Hypersalivation: Increased salivation, which among other etiologies may be caused by clozapine treatment.

Neuroleptic dogma: The firmly held yet incorrect notion that extrapyramidal symptoms are a necessary manifestation of antipsychotic efficacy.

Phase I trials: Trials conducted in small to moderately sized samples of healthy volunteers with the goal of assessing safety of experimental drugs.

Phase II trials: Trials conducted in ill subjects to assess efficacy and for dose-finding purposes, and in larger samples of healthy or ill subjects to expand Phase I safety evidence.

Phase III trials: Pre-marketing randomised controlled trials conducted in larger samples of ill subjects to expand efficacy and safety evidence.

Pseudospecific schizophrenia phenomenon: A clinical symptom common to many disorders and hence, not specific to schizophrenia.

Psychopathology: The study of the origin, development, and manifestations of mental or behavioral disorders.

Tachycardia: Abnormally high heart rate.

Tardive Dyskinesia: Neurological disorder resulting in involuntary, repetitive body movements that may result from prolonged antipsychotic drug treatment.

Treatment-resistant (or refractory): Resistant to conventional treatment.

5.4 Acronyms

APA: American Psychiatric Association

CATIE: Clinical Antipsychotic Trials of Intervention Effectiveness

CNR: Clozaril National Registry

CPMS: Clozaril Patient Management System

CSAN: Clozaril Support and Assistance Network (Canada)

EPS: Extrapyramidal Symptoms

FDA: Food and Drug Administration

FGA: First-generation Antipsychotic

InterSePT: International Suicide Prevention Trial

MHRA: Medicines and Healthcare products Regulatory Agency

NAMI: National Alliance on Mental Illness

NDA: New Drug Application

NICE: National Institute for Clinical Excellence (UK)

NIMH: National Institute of Mental Health

PORT: Patient Outcomes Research Team

pppy: per patient per year

RCT: Randomised Controlled Trial

R&D: Research and Development

sNDA: Supplement to New Drug Application

SGA: Second-generation Antipsychotic

WBC: White Blood Cell

5.5 Timeline of key events

Key:

Canada
UK
US
Other International development (Europe, Japan)

Year	Event
1958	Wander AG synthesises cyclic compounds in search of antidepressants (Switzerland).
1959	Hunziker et al. at Wander AG identify a tricyclic compound initially called HF-1854 (later renamed clozapine) with antipsychotic properties but free of cataleptic effects (Hunziker, Kunzte et al. 1963).
1960	Wander AG obtains a patent for clozapine (Berne, Switzerland)
1962	Wiener Medizinische Wochenschrift publishes a study on the first two human clozapine trials completed: one with negative results (N=12) and the other with promising results (N=28) (Gross and Langner 1966; Bindra and Lednicer 1982). Clinical trial methodology in this era was relatively primitive (Meltzer: Personal Communication 2012).
1966	Positive results observed in trials where nearly 100 patients with schizophrenia had been treated with clozapine (mainly Austria and Germany) lead to a consensus that clozapine is an effective antipsychotic despite its 'atypicality', ie absence of *extrapyramidal side effects* (EPS). This propels the next wave of research (Schmutz and Eichenberger 1982).

1967	Sandoz acquires Wander AG.
Late 1960's	Trials involving ~2200 patients with schizophrenia are conducted in several European countries (Bente, Engelmeier et al. 1967; Berzewski, Helmchen et al. 1969; Gross and Langner 1969; Gross and Langner 1970; Angst, Bente et al. 1971; Angst, Jaenicke et al. 1971; Balassa, Deisenhammer et al. 1971; de Maio 1972; Berwick 2003). These studies begin to build the evidence base of clozapine's antipsychotic efficacy.
November 1970	Sandoz obtains a US patent for clozapine – an important milestone, because during that period market exclusivity in the US was guaranteed for the 17-year period following patent issuance.
1971	Registration of clozapine begins, a first step toward its formal market release in Europe.
Early 1970s	Hippius, a German academic researcher, partners with Stille, a Wander-Sandoz researcher, to challenge the "neuroleptic dogma" with pharmacological and clinical data. They publish two papers in German (Stille and Hippius 1971; Hippius and Stille 1973), but according to Hippius, "response to our results was weak […] pharmacologists and clinicians were too wedded to the notion of an inseparable connection between antipsychotic efficacy and extrapyramidal effect" (Hippius 1999).
1973	Sandoz hires Gil Honigfeld as US Director of research & development for clozapine
1974	Open-label (Phase II) trials are initiated in the US.
1974	Alarming discoveries of orthostatic hypotension and high heart rates are reported among patients treated with clozapine (Crilly 2007).
1974	Clozapine is marketed in West Germany.
1974-75	First RCT, a Phase II trial (N=31), is initiated in the US. The study, published in 1979, showed that 'clozapine was more effective in overall improvement response, discharge rate, and ameliorating symptoms than was chlorpromazine' (Shopsin, Klein et al. 1979).
1974-75	First Phase III trial (multicentre RCT, clozapine vs. chlorpromazine) is

	initiated in the US (study #16). Study #16 recruits patients with intolerance to conventional antipsychotics due to neurological side effects; treatment resistance is not a criterion for inclusion. Study eventually shows that clozapine is superior to chlorpromazine (Claghorn, Honigfeld et al. 1987).
February 1975	Clozapine enters Finnish market (Idanpaan-Heikkila, Alhava et al. 1975).
June-July 1975	Lancet, European Journal of Clinical Pharmacology and other journals publish studies describing the development of agranulocytosis and other severe hematological disorders in 18 Finnish patients, clustered in five of a total of 69 psychiatric hospitals in South and West Finland; nine of them die (Idanpaan-Heikkila, Alhava et al. 1975; Amsler, Teerenhovi et al. 1977; Idanpaan-Heikkila, Alhava et al. 1977).
July 1975	Clozapine is removed from the market in Finland and other European countries (Crilly 2007).
September 1975	Lancet publishes the first report on the 'Finnish epidemic' (Idanpaan-Heikkila, Alhava et al. 1975).
1975 onwards	In European countries where clozapine remains available, the drug is distributed through normal channels. Although Sandoz agrees to not promote the drug and package labelling recommends enhanced blood monitoring (Honigfeld: Personal Communication 2011), monitoring is not enforced (Crilly 2007). Nonetheless, there is a sharp drop in mortality associated with agranulocytosis/other hematological side effects (Leber/U.S. FDA 1989; Hurwitz 1992; Crilly 2007).
1975	The South African Medical Journal publishes earliest evidence of an association between clozapine and weight gain (Hemphill, Pascoe et al. 1975).
1976	Sandoz halts R&D efforts in US and, as a result, ongoing trials are abruptly terminated. This includes several open-label trials, as well as Study #16, which is aborted after recruiting half (151) of its target study sample (Casey/U.S. FDA 1989).
1976 onwards	Clozapine remains available in the US through Sandoz's compassionate need programme. The programme is overseen by Gil Honigfeld, who receives overwhelmingly positive feedback from clinicians, researchers,

	and patients/families (Honigfeld: Personal Communication 2011).
1979	The American Journal of Psychiatry publishes a study showing that clozapine does not increase human prolactin levels (Meltzer, Goode et al. 1979). This study led the authors to conclude that clozapine may achieve its antipsychotic effect differently from older or first generation antipsychotics.
1980-82	After learning through Sandoz's liaison with the US Food and Drug Administration (FDA) that the agency would not be averse to reviewing a new drug application (NDA) for clozapine if the company addressed safety concerns, Gil Honigfeld advocates for the resurrection of the NDA application (Honigfeld: Personal Communication 2011).
1982	Sandoz directors instruct Gil Honigfeld to begin work on an NDA submission under the conditions that it needs to be completed in one year and no additional R&D resources may be used (ie no new trials) (Crilly 2007; Honigfeld: Personal Communication 2011).
April 1983	Sandoz submits NDA based on five clinical trials: four open-label studies conducted during the compassionate use period and Study #16 (Casey/U.S. FDA 1989; Honigfeld: Personal Communication 2011).
February 1984	The Psychopharmacologic Drugs Advisory Committee endorses the decision by the US FDA's Neuropharmacologic Drug Products Division to reject the NDA application for clozapine (Leber/U.S. FDA 1989).
June 1984	After communicating its rejection decision to Sandoz, the US FDA conveys to the company that it might approve clozapine if the company can demonstrate superiority vs standard treatment (Leber/U.S. FDA 1989), as well as effectively address its hematological risks through a method of its own choosing (Honigfeld: Personal Communication 2011).
1984	Shortly thereafter, Sandoz enlists academic researchers to assist its staff in the design of Study #30 (with John Kane as Principal Investigator). The US FDA, represented by Paul Leber (Director of US FDA's Neuropharmacologic Drug Products Division), is actively involved in the design process (Leber/U.S. FDA 1989; Honigfeld: Personal Communication 2011).

1984	Study #30, a six-week double blind RCT (clozapine vs chlorpromazine), begins in 16 centres (N=319); its results are hailed as incontrovertible evidence of clozapine's superiority in a treatment-resistant population.
1984	Hatch-Waxman Act is passed by U.S. Congress, guaranteeing up to a five-year period of market exclusivity for the brand name following NDA approval.
1984	Journal of Clinical Psychopharmacology publishes a paper reporting on the ability of clozapine to alleviate even extremely severe symptoms of tardive dyskinesia (Meltzer and Luchins 1984).
1987	To improve the odds of a successful NDA application, Sandoz's Marketing Department designs the Clozaril Patient Management System (CPMS) – its policy was summarised as 'no blood, no drug' (Honigfeld/U.S. FDA 1989).
1987	Sandoz submits NDA application for its branded product clozaril based on studies #30 and #16.
1987	Journal of Clinical Psychopharmacology publishes study #16 (Claghorn, Honigfeld et al. 1987).
1987-88	Year-long field testing of CPMS (Bastani, Alphs et al. 1989) The field testing fails to expose characteristics of the programme that would eventually lead to its undoing (Honigfeld: Personal Communication 2011).
September 1988	Archives of General Psychiatry publishes Study #30 (Kane, Honigfeld et al. 1988).
February 1989	The US FDA's Psychopharmacologic Drugs Advisory Committee hears the presentations of a divided FDA review team and those of Gil Honigfeld and other Sandoz representatives and consultants. Following a long discussion and despite safety concerns, the Committee unanimously recommends approval of the NDA for treatment-resistant schizophrenia (Casey/U.S. FDA 1989).
September 1989	US FDA approves NDA; product labelling limits availability of clozaril to the CPMS (Hurwitz 1992).
October	The Journal of Pharmacology and Experimental Therapeutics publishes

1989	a study providing evidence underlying the pharmacologic atypicality of clozapine (Meltzer, Matsubara et al. 1989).
January 1990	Clozapine receives product licence in the UK.
February 1990	Clozapine enters US market as a bundled product (CPMS), with brand name clozaril. As a result of its prohibitive price, no payer – public or private - covers the drug (Metzenbaum 1991; Hurwitz 1992; Crilly 2007).
December 1990	Thirty-three states and the District of Columbia bring a class action antitrust law suit against Sandoz in Federal Court (Goodman, Ahn et al. 1997; Crilly 2007).
1990	The New York Times publishes two pieces on advocacy efforts focused on clozapine. One published in September is about a national campaign that aims to force a change in clozaril's marketing system (Goleman 1990). The other published in December is about a request for the US Federal Trade Commission to investigate Sandoz's marketing practices (Freudhiem 1990).
March 1991	The US Senate Subcommittee on Antitrust, Monopolies, and Business Rights convenes a hearing to consider the CPMS bundling issue (Metzenbaum 1991; Crilly 2007).
April 1991	Sandoz unbundles CPMS in the US, relinquishing control of blood testing and distribution and opening up the clozapine market to standard distribution channels (Hurwitz 1992; Crilly 2007). However, the company maintains a major role in hematological safety by agreeing to run the Clozapine National Non-Rechallenge masterfile (Honigfeld: Personal Communication 2011). Unbundling lowers US costs of the drug alone to $4160 per patient per year (Goodman, Ahn et al. 1997).
May 1991	The US Senate Subcommittee issues a ruling in support of Sandoz's decision to unbundle CPMS. In addition, it orders that the company settles the class action suit and that state Medicaid programmes cover the costs of clozapine treatment (Crilly 2007).
May 1991	The US Department of Health and Human Services orders all state Medicaid programmes to pay for clozapine treatment, agreeing in turn to pay for half of the drug and monitoring costs (Crilly 2007).

June 1991	The New York Times publishes an article about clozapine cost and access, stating that 'concerns remain that the drug's manufacturer […] is trying to profiteer from the desperation of mental patients and their families' by denying drugs to patients (NYT Reporter 1991).
December 1991	Clozapine is approved for marketing in Canada. Marketed as clozaril, the drug is available only through a distribution system, Clozaril Support and Assistance Network (CSAN), which ensures weekly blood testing prior to the dispensing of the next period's supply of medication (Clozaril monograph 1991).
1992	Sandoz significantly scales back clozaril marketing resources well before the end (in 1994) of its US five-year exclusivity period (Crilly 2007; Honigfeld: Personal Communication 2011).
September 1994	American Journal of Psychiatry publishes earliest evidence of clozapine's glucoregulatory effects (Kamran, Doraiswamy et al. 1994).
1994	International Pharmaceutical Abstracts publishes earliest evidence of clozapine's lipid effects (Ghaeli 1994).
February 1995	American Journal of Psychiatry publishes a study that found that clozapine was associated with an 85% reduction in suicide attempts over a two year period (Meltzer and Okayli 1995).
1995	Sandoz sponsors an analysis of its patient registry data to investigate troubling findings from the US FDA Spontaneous Reporting System database (Dubitsky/U.S. FDA 2002). A key finding of these analyses is a markedly reduced overall risk of dying associated with clozapine treatment, primarily attributable to lower risk of death by suicide in current versus past clozaril users (Walker, Lanza et al. 1997).
1995	Sandoz submits a supplement to its NDA (sNDA) with the purpose of describing clozaril's anti-suicidal effects in the product labelling and to request an expansion of the drug's indication. The FDA rejects the application (Dubitsky/U.S. FDA 2002).
1996	Sandoz and Ciba-Geigy merge and become Novartis.
1996	Daniel Vasella MD, CEO of Novartis, approves funding for a large international RCT with Herbert Meltzer as Principal Investigator that will assess clozapine's anti-suicidal effects. Vasella's initial motivation for

	funding the trial was to increase sales of clozapine. Although approval of the first generic clozapine seriously undercuts this hope, Vasella approves the trial to go forward on humanitarian grounds (Meltzer: Personal Communication 2012) and a sense of moral obligation (Honigfeld: Personal Communication 2011).
January 1997	Novartis representatives meet with members of the US FDA's Neuropharmacologic Drug Products Division to discuss the protocol of study ABA 451, later renamed InterSePT (Dubitsky/U.S. FDA 2002).
1997	Zenith Goldline Pharmaceuticals (now IVAX Pharmaceuticals) receives US FDA approval for a generic version of clozapine, the first in the US, along with its own patient registry. Even after the market introduction of generic clozapine products and the end of its patent exclusivity, Novartis remains responsible for setting clozapine safety-related policies.
1998	The Schizophrenia Patient Outcomes Research Team (PORT) in the US strongly recommends clozapine for treatment-resistant schizophrenia (Lehman, Steinwachs et al. 1998).
1998	Canadian Psychiatric Association strongly recommends clozapine for treatment-resistant schizophrenia (Canadian Psychiatric Association 1998).
March 1998	First patient enrols in study ABA 451 (later renamed InterSePT study), a two-year multicentre and international RCT that compares risk of suicidal behaviour among patients on clozapine vs olanzapine (N=980).
1998	Journal of Clinical Psychiatry reports on a study that assessed the impact of mandatory blood monitoring on clozapine-related morbidity and mortality (Honigfeld, Arellano et al. 1998). The authors found that compared to the period preceding the implementation of the programme of mandatory blood monitoring, incidence of agranulocytosis and its associated lethality had dropped substantially.
2000	The Psychiatrist publishes a study reporting on geographic variation in clozapine prescribing, which may be due to variation in provider adherence to clinical guidelines (Purcell and Lewis 2000).
October 2000	The Wall Street Journal publishes a piece entitled 'Doctors raise warnings about a form of clozapine --- FDA-approved generic version of schizophrenia drug has disturbing effects in studies', focused on a

	Zenith/IVAX generic clozapine product that may not be bioequivalent to clozaril (Burton 2000).
2001	The US FDA reviews studies' claims of non-bioequivalence (Ereshefsky and Glazer 2001; Kluznik, Walbek et al. 2001) for possible action. While Novartis uses the Ereshefsky study to discourage switches to its generic rival, Zenith/IVAX launches a lawsuit against Novartis, and along with the US Generic Pharmaceutical Association attacks the study in press releases, news reports, and letters to the FDA.
January 2001	Psychiatric Services publishes a study showing that persons who have previously refused to consider a trial of clozapine can be swayed if the facts are presented to them by experienced providers and by patients currently taking the drug (Grace and Szarowicz 2001).
October 2001	Archives of General Psychiatry publishes an NIMH-funded study which found that clozapine was superior to a moderate dose of haloperidol in outpatients with non-severe symptoms refractory to other drugs (Kane, Marder et al. 2001).
2001	Psychological Medicine publishes a qualitative study on patients' views regarding their clozapine treatment (Angermeyer, Löffler et al. 2001). The authors did not find unease over routine blood tests, with patients' negative perceptions mostly centred around fatigue and sedation.
November 2002	The Psychopharmacologic Drugs Advisory Committee discusses the sNDA. The Committee votes 8:1 in favour of Novartis's claim that clozapine is effective in the management of suicidality regardless of patients' responsiveness to treatment (US FDA 2002). They defer to the US FDA on the wording for the indication (US FDA 2002).
December 2002	The US FDA approves the use of clozapine for patients at risk for emergent suicidal behaviour. This is clozapine's second unique indication.
January 2003	Archives of General Psychiatry publishes InterSePT study, which finds a definitive clozapine advantage in reducing suicidal behaviour (Meltzer, Alphs et al. 2003).
2003	Four to six months after gaining US FDA approval for clozapine's suicidality indication, Vasella halts the company's educational/marketing efforts. Vasella halts further marketing of

	clozapine for suicide indication because sales do not warrant the investment (Meltzer: Personal Communication 2012).
February 2003	Generic clozapine enters Canadian markets following clinical trials in Canada under the regulatory supervision of Health Canada. The introduction of clozapine from other manufacturers resulted in the establishment of manufacturer-specific registry and distribution systems (Health Canada 2003).
2003	National Institute for Clinical Excellence (UK) strongly recommends clozapine for treatment-resistant schizophrenia (National Institute for Clinical Excellence 2003).
September 2003	The US FDA issues a letter asking manufacturers of all SGAs available in the US market to add text to the 'warnings' section of the product label stating that epidemiological studies 'suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics'.
February 2004	Diabetes Care publishes a consensus statement containing the recommendation that metabolic screening and monitoring be conducted for patients prescribed SGAs (Anonymous 2004).
February 2004	Alamo pharmaceutical receives NDA approval by the US FDA for commercialisation of orally disintegrating clozapine (brand name Fazaclo).
October 2004	Journal of Clinical Psychiatry publishes a report showing that among patients on established medication regimens, patients' attitudes toward clozapine are similar to attitudes toward other antipsychotics (Freudenreich, Cather et al. 2004).
2004	American Psychiatric Association strongly recommends clozapine for treatment-resistant schizophrenia, as well as suicidality (Lehman, Lieberman et al. 2004).
March 2005	Psychiatric Services publishes a study showing differences in use and dosages of clozapine in two populations with similar diagnoses and demographic characteristics in Maryland, USA and Victoria, Australia (Conley, Kelly et al. 2005).
2005	Canadian Psychiatric Association additionally recommends clozapine

	for suicidality (Canadian Psychiatric Association 2005).
April 2006	McEvoy et al. publish results from phase 2 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), an NIH-funded RCT (McEvoy, Lieberman et al. 2006). The authors reported that clozapine monotherapy was more effective than switching to another SGA among treatment-resistant patients, adding that safety monitoring is necessary to detect and manage clozapine's serious side effects. The authors suggested that systematic efforts be undertaken to expand clozapine use.
May 2008	Psychiatric Services publishes a study on trends in antipsychotic use in the Veterans Administration (Sernyak and Rosenheck 2008). The authors found that while the use of newly marketed antipsychotics had increased, clozapine use had remained flat, at 2.0%—3.0%.
February 2009	Medicines and Healthcare products Regulatory Agency (MRHA) grants Merz Pharma UK Ltd marketing authorisation for two generic clozapine products based on bioequivalence study results. Patients using these drugs must be registered with manufacturer-specific registry and distribution systems (Tomlinson: Personal Communication 2011).
July (online) -August (print) 2009	Finnish investigators publish results of a large cohort study that concluded that 'long-term treatment with antipsychotic drugs is associated with lower mortality compared with no antipsychotic use' (Tiihonen, Lonnqvist et al. 2009). The authors also concluded that SGAs are highly heterogeneous, and that clozapine appears to be associated with a substantially lower mortality than all other antipsychotics.
July 2009	Associated Press publishes a piece entitled 'Study: Clozapine may have saved schizophrenics', which reports on the results of the Finnish cohort study published online. The first lines read 'Thousands of people with schizophrenia worldwide could have been saved if doctors had prescribed them the anti-psychotic drug clozapine, a new study says' (Cheng 2009).

5.6 Narrative

Clozapine was developed in 1959 by Wander AG, a Swiss pharmaceutical company. This discovery happened at the end of a decade marked by the development just a few years earlier of chlorpromazine, the first drug with antipsychotic or neuroleptic properties.

Knowledge of chlorpromazine's mechanism of action led to the belief that a cataleptic effect and apomorphine antagonism were pre-requisites for neuroleptic efficacy (Hippius 1999). Clozapine was not found, however, as a result of a targeted search for a new neuroleptic. Motivated by the discovery in 1957 that tricyclic compounds had antidepressant properties, Wander scientists searched for novel tricyclic antidepressants. Serendipitously, among their discoveries was clozapine, a drug which despite its tricyclic chemical structure behaved like a neuroleptic. The company decided to pursue further studies of this drug, and a patent was submitted in Switzerland in 1960 (Crilly 2007). Although laboratory and animal studies suggested that it had similarities with chlorpromazine, scepticism around its potential efficacy was spurred by the finding that clozapine did not have a cataleptic effect and also by the observation that it was not associated with *extrapyramidal symptoms* (EPS). Because the latter was firmly regarded as a necessary manifestation of antipsychotic efficacy, a view that was later proved to be wrong, Hippius has referred to this belief as the 'neuroleptic dogma' (Hippius 1999).

The first two human trials conducted to assess the efficacy of clozapine were completed in the early 1960s, one yielding negative results (N=12) and the other yielding promising results (N=28) (Gross and Langner 1966; Bindra and Lednicer 1982). Of note, clinical trial methodology in this era was relatively primitive (Meltzer: Personal Communication 2012). By 1966, positive results observed in trials mainly conducted in Austria and Germany, where nearly 100 patients with schizophrenia had been treated with clozapine, led to a consensus that the drug was an effective antipsychotic despite its 'atypicality', ie absence of *extrapyramidal symptoms* (EPS). These results propelled the next wave of research (Schmutz and Eichenberger 1982).

Later that decade, European researchers conducted trials involving around 2200 patients with schizophrenia which established the antipsychotic properties of clozapine despite the absence of EPS (Bente, Engelmeier et al. 1967; Angst, Bente et al. 1971; Angst, Jaenicke et al. 1971; Balassa, Deisenhammer et al. 1971). The first *randomised controlled trial* (RCT) was among them (Angst, Bente et al. 1971). However, clozapine was tepidly received, perhaps because many studies were published solely in German (Hippius 1999) and/or due to widespread scepticism spurred by the firm sway of the neuroleptic dogma (Hippius 1989; Hippius 1999; Crilly 2007). Two chance occurrences may have kept clozapine from being discarded at that early stage (Crilly 2007): (i) the apomorphine gnawing test, which has now become the standard test to screen for neuroleptic efficacy, was not available at that point, as clozapine would have failed it, and (ii) the fact that the drug was erroneously thought to have analgesic properties (an error that resulted from salivation-induced short-circuits in the oral electrodes implanted in test animals).

Thus, clozapine *research and development* (R&D) proceeded although scepticism abounded. The acquisition of Wander AG by Sandoz in 1967 has been described both as a facilitator to clozapine's R&D in that more resources became available (Crilly 2007), and as a barrier in that clozapine lost its profile in a larger organisation (Ackenheil 1977). In 1971, the company began registration of the drug as a first step toward its market release in Europe. Around that time, Hippius, a German academic researcher, partnered with Stille, a Wander-Sandoz researcher, to challenge the neuroleptic dogma with pharmacological and clinical data. They published two papers in German (Stille and Hippius 1971; Hippius and Stille 1973), but according to Hippius, 'response to our results was weak (…),

pharmacologists and clinicians were too wedded to the notion of an inseparable connection between antipsychotic efficacy and extrapyramidal effect' (Hippius 1999).

In the US, after obtaining a patent for clozapine in 1971, Sandoz hired Gil Honigfeld as Director of R&D for clozapine in 1973, and under his leadership, the company launched open label Phase II trials in 1974. It was in the course of one of these trials that Honigfeld and fellow Sandoz researchers observed alarmingly high heart rates and severe orthostatic hypotension among healthy male volunteers in a prison setting (Crilly 2007). At this point, these side effects 'loomed as a nearly insurmountable problem [for approval and marketing purposes]' (Personal Communication: Crilly 2012). However, upon learning of the critical importance of slow titration, Honigfeld and Sandoz researchers, in collaboration with the US *Food and Drug Administration* (FDA), developed a successful treatment strategy to reduce the risk for these cardiovascular events (Crilly 2007). In the view of Gil Honigfeld, this successful collaboration with the FDA earned the company a level of trust that may have facilitated its eventual negotiations with the agency around the drug's hematological risks (Honigfeld: Personal Communication 2011).

The first randomised controlled Phase II trial (N=31) was initiated in the US in 1974–5 under the sponsorship of Sandoz. The study, eventually published in 1979, showed that 'clozapine was more effective in overall improvement response, discharge rate, and ameliorating symptoms than was chlorpromazine' (Shopsin, Klein et al. 1979). Shortly thereafter, the company launched the first randomised controlled Phase III multicentre trial, named *Study #16*. This trial recruited patients with intolerance to conventional antipsychotics due to neurological side effects; treatment resistance was not a criterion for inclusion. The study, eventually published in 1987, also showed that clozapine was superior to chlorpromazine (Claghorn, Honigfeld et al. 1987).

In June–July 1975, only four months after being introduced in the Finnish market, eighteen patients clustered in five (of a total of 69) psychiatric hospitals in South and West Finland developed agranulocytosis and other severe hematological disorders; nine of them died (Idanpaan-Heikkila, Alhava et al. 1975; Amsler, Teerenhovi et al. 1977; Idanpaan-Heikkila, Alhava et al. 1977). This development caught everyone by surprise: until then, the prevalent view was that sedation and hypersalivation were the main side effects of clozapine. The assumption was (if discussed at all) that the drug's potential for hematological side effects was no greater than that observed for other antipsychotics. Alarming reports of cases of clozapine-related agranulocytosis and fatalities began to surface in other countries. Legitimate concern over the seriousness of this side effect led to the withdrawal of clozapine in most of the countries where it was already in the market (Crilly 2007).

In the US, Sandoz halted R&D efforts in 1976. This led to the abrupt termination of all ongoing trials; among them were several open-label trials as well as Study #16, which was aborted after recruiting only half (151) of its target study sample (Casey/FDA 1989). However, clozapine remained available in the US through a compassionate need programme overseen by Gil Honigfeld at Sandoz. This action received an overwhelmingly positive response and feedback from clinicians, researchers, patient advocates as well as patients and their families (Honigfeld: Personal Communication 2011). In the European countries where clozapine remained available, the drug was distributed through normal

channels. Although Sandoz agreed to not promote the drug, and package labeling recommended enhanced blood monitoring (Honigfeld: Personal Communication 2011), monitoring was not enforced (Crilly 2007). Nonetheless, there was a sharp drop in mortality associated with agranulocytosis and other hematological side effects (Leber/FDA 1989; Hurwitz 1992; Crilly 2007).

Despite the relative blackout on clozapine sales around the world, researchers continued to conduct studies on its pharmacology, efficacy, and safety. In 1975, the South African Medical Journal published the earliest evidence of an association between clozapine and weight gain (Hemphill, Pascoe et al. 1975). In the US, Herbert Meltzer and colleagues showed that clozapine spares blockade of key dopamine receptors, thus demonstrating for the first time a general characteristic of almost all *second-generation antipsychotics* (SGAs) whose corollary was that sustained prolactin increases are not essential for antipsychotic action (Meltzer, Goode et al. 1979). This study was important because its findings led the authors to conclude that clozapine may achieve its antipsychotic effect differently than the older, *first-generation antipsychotics* (FGAs).

Between 1980 and 1982, after learning through Sandoz's liaison to the FDA that the agency would not be averse to reviewing a *new drug application* (NDA) for clozapine if the company addressed safety concerns, Gil Honigfeld began advocating for the resurrection of the NDA application (Honigfeld: Personal Communication 2011). In 1982, Sandoz directors instructed Gil Honigfeld to begin work on an NDA submission under the conditions that it needed to be completed in one year and with no additional R&D resources (Crilly 2007; Honigfeld: Personal Communication 2011). In April 1983, Sandoz submitted an NDA based on five clinical trials: four open-label studies conducted during the compassionate use period, and just one Phase III trial (Study #16). Although the latter trial had been halted prior to being completed, Sandoz conducted analyses of the data in their possession and found that in a treatment-intolerant population, clozapine was superior to chlorpromazine (Casey/FDA 1989). In February 1984, the FDA Psychopharmacologic Drugs Advisory Committee endorsed the decision by the agency's Neuropharmacologic Drug Products Division to reject the application based on their assessment that the '1% incidence of agranulocytosis among patients treated for 6 months (…) was an absolute and intolerable barrier to the marketing of a drug that had no proven superiority to existing and (then) marketed neuroleptics' (Leber/FDA 1989).

After communicating its decision to Sandoz in June that year, the FDA entered 'into proactive negotiations with Sandoz to try to convince them' that what appears as a negative outcome 'was not as negative as it might appear in one reading.' In fact, the committee had said that the drug could be approved, despite 'the presence of a very terrifying rate of agranulocytosis, provided the evidence of efficacy in a special treatment-resistant population could be adduced' (Leber/FDA 1989). Although active control trials are not a standard regulatory requirement, the FDA communicated in these negotiations that approval would be contingent on a demonstration of superiority versus standard treatment in both efficacy and EPS tolerability (Leber/FDA 1989). This demand was contested by Sandoz, but the FDA was unrelenting. Moreover, the agency also communicated that approval would be unlikely unless Sandoz had devised an acceptable method to specifically address clozapine's hematological risks (Leber/FDA, 1989). Despite their requests for

clarification, Sandoz did not receive guidance from the FDA on what constituted an acceptable method.

Shortly thereafter, Sandoz enlisted academic researchers, with John Kane as Principal Investigator, to assist its staff in the design of a trial that would meet the regulators' approval requirements; the trial was named *Study #30*. The FDA, represented by Paul Leber (Director of the agency's Neuropharmacologic Drug Products Division), was actively involved in the design process (Leber/ FDA, 1989). Thomas Laughren, the Division's deputy director, was also actively involved (Leber: Personal Communication 2012). Study #30 began recruiting a target sample of 319 patients not long after that (Kane, Honigfeld et al. 1988). The study was a six-week multicentre double blind RCT. It assessed the efficacy of clozapine relative to chlorpromazine in inpatients with schizophrenia considered to be treatment-resistant by history and prospective study, and who in addition met stringent severity criteria. The prospective study was a six-week trial with another antipsychotic (haloperidol) that was completed prior to randomisation into the active trial. According to Gil Honigfeld, this study was important methodologically because of its rigorous criteria for identifying treatment-resistant patients (Honigfeld: Personal Communication 2011).

Also in 1984, the US Congress passed the Hatch-Waxman Act, which guaranteed a period of up to five years of market exclusivity for the branded drug following NDA approval. Although this was advantageous to Sandoz in that up until then, US law guaranteed exclusivity for the seventeen-year period following patent issuance (ie 1988 for clozapine), the timing of the passage of Hatch-Waxman makes it implausible that the Act motivated the company to seek the NDA.

Research on the drug's safety profile was expanded in 1984 when Herbert Meltzer and colleagues published a paper reporting on the ability of clozapine to alleviate even extremely severe symptoms of tardive dyskinesia (Meltzer and Luchins 1984).

To improve the odds of a successful NDA application, Sandoz's Marketing Department designed in 1987 the *Clozaril Patient Management System* (CPMS), the company's response to the FDA's demand for an acceptable method to address clozapine's hematological risks. The basic tenet of CPMS was that clozapine treatment would be contingent on weekly monitoring of *white blood cell* (WBC) counts ('no blood, no drug'). CPMS was designed to mimic the success of the WBC monitoring built into Sandoz pre-marketing investigational program (96% overall), while improving on the observed drop in compliance rate with the recommended schedule which fell to 78% in the second six months of their trials (Honigfeld/FDA 1989). Although the company conducted a year-long field testing of CPMS in 1987–8 (Bastani, Alphs et al. 1989), the field testing failed to expose characteristics of the programme that would eventually lead to its undoing (Honigfeld: Personal Communication 2011).

Shortly after beginning the design of the CPMS program, also in 1987, Sandoz submitted an NDA application for its branded product Clozaril mainly based on studies #30 and #16; the NDA application contained only an outline of the programme.

In February 1989, with Daniel Casey chairing, the FDA's Psychopharmacologic Drugs Advisory Committee heard the presentations of a divided FDA review team and those of

Sandoz representatives (including Jack Singer, R&D Director and Gil Honigfeld) and researchers/scientists presenting on behalf of Sandoz (John Kane and Herbert Meltzer among them). Paul Leber introduced the FDA presentations and actively probed meeting attendants. Richard Kapit, the agency's safety data review expert, recommended against approval due to unacceptable risks, while Thomas Laughren, team leader, cautiously recommended approval ('In looking at both the safety and the efficacy data, I am inclined to think that clozapine does offer a benefit that overcomes its risks even though those risks are, admittedly, substantial […] I want to emphasize that despite my inclination to recommend the approval of clozapine, I am still uneasy about this recommendation'). Meeting attendants engaged in a lively and in-depth discussion of the efficacy and safety of clozapine and of the value of CPMS; it was during this part of the discussion that Daniel Casey stated 'the consensus of the Committee [is that] the monitoring system will be valuable. It will probably produce information that we do not yet know it will produce. But it is not the critical issue in assessing the risk-benefit ratio' (Casey/FDA 1989). Following this discussion, the Committee unanimously recommended approval of the NDA application 'for the claimed indication of treatment-resistant schizophrenia in the face of the substantial risks associated with its use' (Casey/FDA 1989). Later that year, on 26 September, the FDA officially approved the NDA, its product labeling limiting availability of the drug to the CPMS (Hurwitz 1992).

Research on the drug's pharmacological properties conducted by Meltzer and colleagues and published in 1989 provided evidence underlying clozapine's pharmacologic atypicality (Meltzer, Matsubara et al. 1989). In the view of its first author, this study was important because it provided a template for the pharmaceutical industry to manufacture other SGAs such as risperidone (Meltzer: Personal Communication 2012).

By the time Clozaril entered the US market on February 5 1990, it did as a highly controversial bundled CPMS product. For its national roll-out, Sandoz contracted with a national home healthcare company to draw blood samples and distribute the drug, and with a national laboratory for analyses and reporting of results. All Clozaril users were required to be registered with the *Clozaril National Registry* (CNR), which collected all clinical data generated in connection with Clozaril treatment. To ensure that the patient's WBC count complied with pre-determined parameters consistent with an expert-based assessment of minimal hematological risk, release of the following week's supply of medication occurred only after blood was drawn.

The cost of the bundled product was $172 per week, which resulted in a cost of approximately $9,000 *per patient per year* (pppy)(1990 prices), making clozapine therapy approximately eight to fifteen times more expensive than therapy with traditional antipsychotics (Tokarski 1990). Notably, the drug itself was responsible for slightly less than half of that amount ($4,150). As a result of its prohibitive price, no payer – public or private – covered the drug (Metzenbaum 1991; Hurwitz 1992; Crilly 2007). This in turn led to a loud public outcry from patients/advocates, psychiatric professionals, potential institutional buyers, and foreclosed competitors (Metzenbaum 1991; Hurwitz 1992; Crilly 2007). As reported in the *New York Times*, patients and their advocates started a national campaign to force a change in the marketing system (Goleman 1990), also asking the US Federal Trade Commission to investigate Sandoz's marketing practices (Freudhiem 1990).

In March 1990, the state of Minnesota launched an antitrust investigation into Sandoz's decision to bundle Clozaril with the monitoring programme. By June, seven other states had joined, and in December, 33 states and the District of Columbia brought a class action antitrust law suit against Sandoz in Federal Court (Goodman, Ahn et al. 1990; Crilly 2007). As a result of these developments, the US Senate Subcommittee on Antitrust, Monopolies, and Business Rights convened a hearing to consider the CPMS bundling issue on 5 March 1991 (Metzenbaum 1991; Crilly 2007). In response to these developments, Sandoz decided to unbundle CPMS, entrusting Gil Honigfeld with the responsibility of overseeing the unbundling project (Honigfeld: Personal Communication 2011). The company relinquished control of blood testing and distribution in April 1991 and opened up the clozapine market to standard distribution channels (Hurwitz 1992; Crilly 2007). From that point onwards, providers were allowed to use their own laboratories, and pharmacies were allowed to dispense Clozaril as long as they used a failsafe system that, like CPMS, ensured the 'no blood, no drug' dictum. However, the company maintained a major role in hematological safety by agreeing to run the Clozapine National Non-Rechallenge masterfile (Honigfeld: Personal Communication 2011). Unbundling halved US costs of the drug, to $4160 pppy (1990 prices) (Goodman, Ahn et al. 1997).

In May 1991, the US Senate Subcommittee ruled that both Sandoz and State Medicaid agencies were at fault for creating barriers to accessing clozapine. Although the Subcommittee supported Sandoz's decision to unbundle CPMS, it ordered the company to pay $30 million to settle the class action suit. Also in May 1991, the US Department of Health and Human Services ordered all State Medicaid agencies to pay for clozapine treatment, agreeing in turn to pay for half of the drug and monitoring costs (Crilly 2007). However, scepticism about Sandoz's willingness to make Clozaril more widely available remained. This was exemplified by a piece that appeared in the *New York Times* in June 1991 which stated that 'concerns remain that the drug's manufacturer, Sandoz Pharmaceuticals, is trying to profiteer from the desperation of mental patients and their families' by denying drugs to patients ('Clozapine's Price, and Value', 1991).

Outside of the US, Sandoz obtained regulatory approval to market clozapine in the UK in January 1990, and in Canada in December 1991, under the brand name Clozaril in both countries. In the UK, the Committee on Safety of Medicines, part of the *Medicines and Healthcare products Regulatory Agency* (MHRA), reviewed the evidence presented by Sandoz in support of its license application, and issued a Medical Assessment Report dated 22 December 1989. Although the MHRA would not disclose specifics on such evidence, and the report had been redacted to keep that information confidential, it appears that Sandoz sought UK approval using the same studies it had used to request approval in the US. Some of the guidelines contained in the original document have been modified. For example, while the original report stated that 'The mandatory safety scheme run by the company to monitor white blood cell count has been planned carefully but will require diligence and enthusiasm to ensure effectiveness [and] it cannot be enforced as a condition of the license', for many years now, clozapine treatment in the UK has required mandatory monitoring of blood counts. All prescribers and patients have to be registered with the UK's Clozaril Patient Monitoring Service, which provides for the centralized monitoring of patients' WBC counts. In Canada, the drug was available only through a closed

distribution system, the Clozaril Support and Assistance Network (CSAN), which ensured weekly blood testing prior to the dispensing of the next period's supply of medication (Clozaril monograph 1991).

In 1992, Sandoz significantly scaled back Clozaril marketing resources, two years before the end of its exclusivity period (Crilly 2007; Honigfeld: Personal Communication 2011). Although pharmaceutical companies typically start to wind down operations in the last one to two years of the exclusivity period in preparation for generic entrants, Sandoz's decision may have been motivated by the high legal costs incurred by the company in connection with the bundled product, costs which may have cut into the company's marketing resources (Crilly 2007). Gil Honigfeld objected, to no avail, on the grounds that Clozaril had brand name loyalty (Crilly 2007; Honigfeld: Personal Communication 2011).

With the greater availability of the drug, new evidence began to emerge on the drug's metabolic side-effects. The earliest published study of clozapine's effects on glucose regulation was published in 1994, when US researchers reported on a case of severe, sustained hyperglycemia associated with high-dose clozapine (Kamran, Doraiswamy et al. 1994). Also that year, US researchers published a study suggesting that clozapine was associated with an increase in serum triglyceride levels, the earliest evidence of clozapine's effects on lipid regulation (Ghaeli 1994).

In 1995, Herbert Meltzer and Ghadeer Okayli published a study of 88 treatment-resistant clozapine-treated patients with schizophrenia whom they prospectively evaluated for suicidality for periods of six months to seven years (Meltzer and Okayli 1995). The authors concluded that their findings suggested that clozapine markedly reduced suicidality. Herbert Meltzer was motivated to conduct this study to confirm a suspicion born from his clinical and research experience that clozapine may have anti-suicidal effects (Meltzer: Personal Communication 2012). Later that year, the US FDA Spontaneous Reporting System database generated some evidence of an increase in all-cause mortality due to cardiovascular events and increased incidence of pulmonary embolism associated with the use of Clozaril. To investigate these findings, Sandoz contracted with Epidemiology Resources Inc to analyse CNR data and assess overall and cause-specific mortality in current and former Clozaril users with schizophrenia (Dubitsky/FDA 2002). A key finding of these analyses was a markedly reduced overall risk of dying during Clozaril treatment, primarily attributable to a markedly reduced risk of death by suicide in current versus past Clozaril users (Walker, Lanza et al. 1997). Prompted by these two studies, Sandoz submitted a supplement to its existing NDA (sNDA) later that year. Their goal was to obtain permission to describe Clozaril's purported anti-suicidal effects in the product labeling and to request that the FDA 'consider expanding the indication for Clozaril (ie for any schizophrenic patient, regardless of neuroleptic-responsiveness, who exhibits suicidality or hopelessness)' (Dubitsky/FDA 2002). Thomas Laughren reviewed the submission on behalf of the FDA, and based on his assessment that neither study had used a randomised design, the agency rejected the application (Dubitsky/FDA 2002).

In 1996, Daniel Vasella, CEO of Novartis (the company that resulted from the merger of Sandoz and Ciba-Geigy), approved funding for an RCT with Herbert Meltzer as Principal Investigator. The primary scientific goal of this study was to provide randomised evidence of clozapine's effects on suicidality (ie anti-suicidal effects), and thus rule out the possibility

that clozapine's lower suicide rate was due to increased clinical contact associated with the need for monitoring (Meltzer: Personal Communication 2012). Although the initial motivation for seeking a second indication was the hope that such indication would lead to wider use of clozapine, the approval during that time of the first generic clozapine product sharply reduced the prospects of commercial gains. Undeterred, Vasella approved the trial to go forward based on humanitarian concerns (Meltzer: Personal Communication 2012) (Honigfeld: Personal Communication 2011).

In January 1997, Sandoz representatives met with members of the FDA's Neuropharmacologic Drug Products Division to discuss the protocol of the trial designed to assess clozapine's anti-suicidal effects (*Study ABA 451*); Meltzer and Walker attended as Sandoz consultants (Dubitsky/FDA 2002). Key among the agency's several concerns was that 'suicidality among patients with schizophrenia may be a pseudospecific phenomenon (ie a clinical symptom common to many disorders that is specific to schizophrenia in name only…),' in which case, 'a new indication would not be allowed' (Dubitsky/FDA 2002). According to Herbert Meltzer, Sandoz representatives did not walk away from the meeting, discouraged by this clarification, because his argument that 'suicide was a separate dimension of the illness, related to other issues such as hopelessness, cognitive impairment, and depression, and not an integral part of psychosis' swayed Paul Leber, who eventually stated that an indication might be approved if the study proved its primary end point (Meltzer: Personal Communication 2012; Personal Communication: Meltzer 2012). Paul Leber participated in the design of the study, and although he resigned his post before the study was completed, his successor Thomas Laughren applied the same criterion for approval (Meltzer: Personal Communication 2012). Study ABA 451, later renamed InterSePT, was designed as a two-year multicentre and international RCT (N= 980) that compared risk of suicidal behavior among patients on clozapine versus olanzapine, another SGA. Enrollment began a year later, in March 1998.

In 1997, the FDA approved the first generic version of clozapine manufactured by Zenith Goldline Pharmaceuticals (now IVAX Pharmaceuticals), along with its own patient registry. Importantly, Novartis remained responsible for setting clozapine safety-related policies even after the market introduction of generic clozapine products and the end of its patent exclusivity,

Evidence on the effectiveness of the hematological monitoring program was published in 1998, when Gil Honigfeld and colleagues reported on analyses of CNR data for the five-year period following the introduction of clozapine in the US (1990–94) (Honigfeld, Arellano et al. 1998). The authors found that, compared to the period preceding the implementation of the program of mandatory blood monitoring, incidence and lethality of agranulocytosis had dropped substantially, from 1–2% to 0.4% for the former, and from 50% to 3% for the latter.

Clozapine's unique role in the treatment of schizophrenia was recognised by developers of clinical practice guidelines. In 1998, both the Schizophrenia *Patient Outcomes Research Team* (PORT) in the US (Lehman, Steinwachs et al. 1998), and the Canadian Psychiatric Association (Canadian Psychiatric Association 1998) strongly recommended clozapine for treatment-resistant schizophrenia. Not all physicians were convinced of the value of clozapine, however. In 2000, UK researchers published a study reporting on geographic

variation in clozapine prescribing, which they attributed to variation in provider adherence to clinical guidelines (Purcell and Lewis 2000).

In October 2000, the Wall Street Journal published a piece entitled 'Doctors raise warnings about a form of clozapine: FDA-approved generic version of schizophrenia drug has disturbing effects in studies' (Burton 2000). The piece was motivated by claims of non-bioequivalence of the Zenith/IVAX generic clozapine product made in studies published the following year which showed that switch to the generic product was associated with clinical deterioration (Ereshefsky and Glazer 2001; Kluznik, Walbek et al. 2001). In 2001, the US FDA reviewed the studies' claims for possible action (http://www.psychiatrictimes.com/display/article/10168/49811). The pharmaceutical companies soon jumped in the fray. While Novartis used the Ereshefsky & Glazer study to discourage switches to its generic rival, Zenith/IVAX launched a lawsuit against Novartis, and along with the US Generic Pharmaceutical Association, attacked the study in press releases, news reports, and letters to the FDA (http://www.medscape.com/viewarticle/406793).

In 2001, the patient perspective regarding clozapine treatment was clarified with the publication of two studies. US researchers reported on a study showing that persons who have previously refused to consider a trial of clozapine may be swayed if the facts are presented to them by experienced providers and by patients currently taking the drug (Grace and Szarowicz 2001). For their part, European researchers reported on a qualitative study that failed to register patient unease over routine blood tests, any negative perceptions mostly centered around fatigue and sedation and not around blood tests or weight gain (Angermeyer, Löffler et al. 2001).

Further evidence on the efficacy of clozapine was published in October 2001, when John Kane and colleagues reported on the results of a NIMH-funded study which had found that clozapine was superior to a moderate dose of an FGA (haloperidol) in partially responsive, community-based patients with moderate symptoms (Kane, Marder et al. 2001).

In February 2002, the same month that InterSePT researchers submitted a manuscript reporting their finding that clozapine was superior to olanzapine in the management of suicidal behavior (Meltzer, Alphs et al. 2003), Novartis submitted an sNDA to the FDA requesting a new indication for Clozaril based on InterSePT results and other data. The sNDA was discussed in November that year by the Psychopharmacologic Drugs Advisory Committee (FDA 2002; Meltzer, Alphs et al. 2003). The Committee voted eight to one on a motion stating that the evidence presented by Novartis provided 'sufficient basis for a new claim involving suicidality in patients with schizophrenia or schizoaffective disorder' regardless of their responsiveness to treatment (FDA 2002). The Committee deferred to the FDA on the wording for the indication (FDA 2002).This was the first time the FDA's Neuropharmacologic Drug Products Division approved a drug for use in schizophrenia that was not based on the drug's ability to produce greater improvement in psychopathology than placebo, effectively ending the FDA policy on 'pseudo-specificity' and opening the door for industry to seek approvals for specific symptom components of schizophrenia, especially cognitive dysfunction (Meltzer: Personal Communication 2012). In December 2002, the FDA approved the use of clozapine for patients at risk for

emergent suicidal behavior, clozapine's second unique indication. In 2003, four to six months after gaining FDA approval for the suicidality indication, Dan Vasella halted Novartis' educational/marketing efforts to promote the new indication. According to Herbert Meltzer, Vasella's decision was prompted by disappointing sales figures and his assessment that the investment was not warranted (Meltzer: Personal Communication 2012). Vasella was not swayed by the pleas of Honigfeld or Meltzer's (Honigfeld: Personal Communication 2011).

It is unclear whether clozapine's hold on the antipsychotic market may have been further eroded by the FDA's decision in September 2003 to issue a letter asking that all SGA manufacturers with a presence in the US market add text to the 'WARNINGS' section of the product label stating that epidemiological studies 'suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics.' Later that year, the American Diabetes Association, the *American Psychiatric Association* (APA), and other professional organisations developed a consensus statement containing the recommendation that metabolic screening and monitoring be conducted for all patients prescribed SGAs; the consensus statement was published in 2004 (Anonymous 2004).

Despite the FDA warning, guideline developers continued to recommend clozapine for people with schizophrenia based on their assessment that its benefits exceeded its risks for selected subpopulations. In 2003, the National Institute for Clinical Excellence (NICE) in the UK strongly recommended clozapine for treatment-resistant schizophrenia (National Institute for Clinical Excellence 2003). In 2004, the APA strongly recommended the drug for treatment-resistant schizophrenia as well as suicidality (Lehman, Lieberman et al. 2004). A year later, the Canadian Psychiatric Association additionally recommended clozapine for suicidality (Canadian Psychiatric Association 2005).

In 2003, generic clozapine products entered Canadian markets following clinical trials in Canada under the regulatory supervision of Health Canada. The introduction of clozapine from other manufacturers resulted in the establishment of manufacturer-specific registry and distribution systems (Health Canada 2003)(Tomlinson: Personal Communication 2011).

In 2004, the gamut of clozapine products commercially available in the US was further expanded with FDA approval of an NDA for orally disintegrating clozapine (brand name Fazaclo) manufactured by Alamo Pharmaceutical.

The evidence on the patient perspective was enriched in 2004 with the publication of a study showing that among patients on established medication regimens, attitudes toward clozapine were no worse than attitudes toward other antipsychotics (Freudenreich, Cather et al. 2004). The evidence on unwarranted variations in the use of clozapine was also expanded with the publication in 2005 of a study which found use differences between two populations with similar clinical and demographic characteristics in Maryland, USA and Victoria, Australia (Conley, Kelly et al. 2005). Although authors were unable to explain their results empirically, they stated that differences in prescribing behaviour among cultures may be driven by differences in pharmaceutical marketing practices and costs (Conley, Kelly et al. 2005). The publication in 2006 of phase two results of the NIH-funded *Clinical Antipsychotic Trials of Intervention Effectiveness* (CATIE) study confirmed

the superiority of clozapine in a treatment-resistant population (McEvoy, Lieberman et al. 2006). CATIE investigators called for safety monitoring to detect and manage clozapine's serious side effects, and for the development of models of service delivery that would encourage clozapine's greater use. An editorial accompanying the release of these findings stated that clozapine 'is our most effective drug for schizophrenic psychosis' and 'the only rational alternative [when other antipsychotic treatments have failed]', referring to authors' calls for systematic efforts to expand its use as 'an idea that is certainly timely' (Tamminga 2006).

In 2008, researchers affiliated with the US Veterans Administration shed further light on the low levels of use of clozapine in the US with the publication of a study on trends in antipsychotic use among veterans (Sernyak and Rosenheck 2008). The authors found that while the use of newly marketed antipsychotics had increased overtime, clozapine use had remained flat, at 2.0—3.0%.

In 2009, the UK's MHRA granted Merz Pharma UK authorisation to market generic clozapine products based on results of a bioequivalence study. The assessment process was augmented through consideration of the application by the National Expert Advisory Group at that time (Tomlinson: Personal Communication 2011). Patients prescribed either of the two generic forms of clozapine used by the National Health Service (Denzapine and Zaponex) have to be registered with the Denzapine Patient Monitoring Service or the Zaponex Treatment Access System, respectively.

In 2009, Finnish investigators published results of a large cohort study, the main finding of which was that long-term treatment with antipsychotic drugs was associated with lower mortality compared with no antipsychotic use (Tiihonen, Lonnqvist et al. 2009). Additionally, the authors found that clozapine appeared to be associated with a substantially lower mortality than all other antipsychotics. The latter results were amplified by the Associated Press through a news piece published in July 2009, the first lines of which were 'Thousands of people with schizophrenia worldwide could have been saved if doctors had prescribed them the antipsychotic drug clozapine, a new study says' (Cheng 2009). Among the reactions of observers not involved in the study was that of James MacCabe, consultant psychiatrist at the National Psychosis Unit at South London and Maudsley Hospital, who stated 'There is now a case to be made for revising the guidelines to make clozapine available to a much larger proportion of patients.' Also cited was Lydia Chwastiak, at the Department of Psychiatry at Yale University, who stated 'If this drug can help people live longer, we need to look seriously at the barriers to using it.' The piece also cited Jari Tiihonen, the study's first author, who stated that the pharmaceutical industry is partly to blame for why clozapine has often been overlooked, 'Clozapine's patent expired long ago, so there's no big money to be made from marketing it.'

5.7 Observations

Some of the factors that may have acted as barriers to the development and adoption of clozapine include:

- The timing of the discovery of clozapine, given the state of the knowledge and preconceptions that held sway in the late 1950s and early 1960s. Key among them was the belief that all antipsychotic drugs must cause extra-pyramidal symptoms.
- The Finnish epidemic, a clustering of highly lethal cases of agranulocytosis in June–July 1975 (Crilly: Personal Communication 2012).
- The implementation of routine patient monitoring schemes – voluntary in some countries, mandatory in others – in tandem with the release of the drug to the market, which caused a higher burden to patients, physicians and systems of care.
- Early on in the US, the high cost of the bundled drug-monitoring system product (CPMS). The costly bundled product significantly limited access to the drug, and as a result of the public outcry and legal challenges that ensued, the drug's manufacturer paid a steep price, both financially and in terms of public relations.
- The manufacturer's decision to terminate promotional and marketing efforts in connection with the two FDA indications. While in the case of the first indication, this decision may have been motivated by the financial drain associated with the problematic reception of CPMS (Crilly 2007), in the case of the second indication, the decision may have been motivated by unimpressive sales figures (Meltzer: Personal Communication 2012).
- The limited tools available for assessing suicidality risk in persons with schizophrenia (Crilly: Personal Communication 2012).

Some of the factors that may have facilitated the development and adoption of clozapine include:

- The small but passionate contingent of advocates, which included researcher-clinicians whose patients benefitted from clozapine (John Kane, Herbert Meltzer), a key industry representative (Gil Honigfeld), and patient advocates.
- Gil Honigfeld's collaborative relationship with FDA representatives, whose foundation may have been built around their successful collaboration to address clozapine's risk for dangerous cardiovascular events (Honigfeld: Personal Communication 2011).
- Paul Leber's active involvement in the design of Study #30, and his support for the company's R&D efforts immediately prior and during the NDA application process, although Leber contends that he was simply following standard FDA procedures (Leber: Personal Communication 2012)(Honigfeld: Personal Communication 2011; Kane: Personal Communication 2012).
- The decision by the FDA that approval of the NDA application would be contingent on the drug demonstrating superiority, a demand contested by Sandoz but ultimately, a key factor in its eventual approval (Honigfeld: Personal Communication 2011).
- The pharmaceutical company's decision to fund an RCT aimed at providing definitive evidence of clozapine's anti-suicidal effects.

- Despite the FDA's historical stance on 'pseudo-specificity', Paul Leber's decision to consider granting approval for clozapine's anti-suicidal effects, and his involvement in the design of the InterSePT study (Meltzer: Personal Communication 2012).

5.8 Other observations of relevance to this case study

It is commonly thought that the main barrier to the broader uptake of clozapine is its adverse effect profile. Although little empirical research exists on the contribution of factors related to physicians, the organisational context (including the marketing environment) and patients, these factors are likely to play a role as they do with other healthcare innovations (Greenhalgh, Robert et al. 2004).

There are no studies that have assessed the contribution of physician factors to the low use of clozapine. However, it has been suggested that insufficient physician knowledge on the effectiveness of the monitoring program prompts unfounded concerns over malpractice litigation (Sherman 2005). This view is supported by the fact that despite the dramatic improvement in its safety profile, the risk of agranulocytosis continues to be cited as a likely determinant of low rates of use of clozapine (Stroup, McEvoy et al. 2004; Meltzer 2005). Physician factors are critical in the view of John Kane. Many physicians are fearful of using clozapine, because of the potential risks and the need for monitoring. Some physicians might not be fully aware of the evidence, or appreciate the potential benefit that some patients can experience, a phenomenon that may be related to the lack of pharmaceutical marketing, as well as the lack of unbiased educational initiatives such as academic detailing. While some physicians will work hard to help a patient experience the potential benefits, others will never discuss the possibility or present it in such a way as to discourage the patient (Kane: Personal Communication 2012).

The contribution of organizational factors to the low use of clozapine is similarly unstudied. As suggested by John Kane and Jari Tiihonen, the absence of pharmaceutical marketing is likely to be an important factor, particularly in the context of active marketing of other antipsychotics. The additional burden to patients, physicians and systems of care associated with the monitoring program is also likely to be implicated; this overall 'hassle' factor is hard to quantify and hard for physicians to acknowledge (Kane: Personal Communication 2012). However, there are pronounced variability in rates of clozapine use across settings with similar monitoring requirements (eg US and Australia [Conley, Kelly et al. 2005]), within the same US health care system (Leslie and Rosenheck 2005), and communities within a UK region (Purcell and Lewis 2000). Such evidence argues against the monitoring program being a principal factor in the low use of clozapine (Hayhurst, Brown et al. 2003).

Last, it has been suggested that low use of clozapine is driven by patients' dislike for the frequent blood tests required by the monitoring programme (Meltzer and Fatemi 1995). Although a plausible barrier, there is no evidence in support of this notion or, more generally, in support of the contribution of patient preferences or attitudes to the low use of clozapine.

1958

1958 Wander AG synthesizes cyclic compounds in the search of antidepressants (Switzerland)

1959 Hunziker et al. at Wander AG identify a tricyclic compound (HF-1854) with neuroleptic properties but free of cataleptic effects (clozapine)

1960

1960 Wander AG obtains a patent for CLOZ (Switzerland)

1962 First 2 human trials are completed :one with negative results (N=12) and the other with promising results (N=28)

1966 Positive results in trials where nearly 100 patients with schizophrenia are treated with CLOZ (Austria, Germany) lead to consensus that CLOZ is an effective antipsychotic despite its atypicality. Prompts next wave of research.

1967 Sandoz acquires Wander AG

Late 1960s Trials involving 2200 patients with schizophrenia are conducted in Switzerland, Austria, Germany, and Italy; among them is the first RCT.

1970

1971 Registration of CLOZ begins, a first step toward its formal market release (Europe)

Early 1970s Hippius, a German academic researcher, partners with Stille, a Wander-Sandoz researcher, to challenge the "neuroleptic dogma" with pharmacological and clinical data. They publish 2 papers in German which receive a poor response.

1973 Sandoz hires Gil Honigfeld PhD as Director of R&D for CLOZ (US)

1970. Sandoz obtains a patent for CLOZ in US

1974 Open-label (Phase II) trials are initiated in the US

1974 CLOZ marketed in W. Germany

1974-1975 First Phase III trial (multicenter RCT, clozapine vs. chlorpromazine [CPZ]) is initiated in the US (Claghorn trial).

1974-1975 Alarming discoveries of orthostatic hypotension and high heart rates are reported among patients treated with clozapine, even at low doses.

1974-75 First RCT is initiated in the US

1975

1975 CLOZ enters Finland market

1975 18 Finnish patients clustered in 5 of a total of 69 psychiatric hospitals in South and West Finland develop agranulocytosis [agran] and other severe hematological disorders; 9 of them die.

1975 onwards European countries where CLOZ remains available, the drug is distributed through normal channels; although monitoring is voluntary, there is a sharp drop in mortality associated with agran/other hematological side effect.

1976 Sandoz halts R&D efforts in US, and as a result, ongoing trials are abruptly terminated.

1976 onwards. CLOZ remains available in the US through Sandoz's compassionate need program overseen by Gil Honigfeld; Honigfeld receives an overwhelmingly positive feed-back from clinicians, researchers, and patients/ families.

1975 The South African Medical Journal publishes earliest evidence of an association between clozapine and weight gain.

1975 First report on the "Finnish epidemic" is published in Lancet.

1975 CLOZ is removed from the market in Finland and other European countries

1980-82 Honigfeld advocates for the resurrection of the NDA application.

1980

1982 Sandoz directors instruct Honigfeld to begin work on an NDA submission under the conditions that it needs to be completed in 1 year and no additional R&D resources may be used (i.e., no new trials)

1983 Sandoz submits NDA based on 5 clinical trials: 4 open-label studies conducted during the compassionate use period, and Study #16.

1984 Passage of Hatch-Waxman Act by US Congress guarantees a 5-yr period of market exclusivity for the brand name following NDA approval.

1984 The Psychopharmacologic Drugs Advisory Committee endorses the decision by the FDA's Psychopharmacologic Drugs Division to reject the NDA application.

1984 Study #30, a 6-week double blind RCT (CLOZ vs. CPZ), begins in 16 centers (N=319); its results are hailed as incontrovertible evidence of CLOZ's superiority in a treatment-resistant population.

1984 Shortly thereafter, Sandoz starts designing Study #30; the FDA, represented by Paul Leber MD (Director of FDA's Psychopharmacologic Drugs Division), is actively involved in the design process

1984 After communicating its decision to Sandoz, the FDA conveys to the company that it might approve CLOZ if the company can demonstrate superiority vs. standard treatment, as well as effectively address its hematological risks through a method of its own choosing.

1987

1987-88 Year-long field testing of CPMS [Bastani et al, '89]; the field testing fails to expose the problematic characteristics of the program that would eventually lead to its undoing.

1987 To improve the odds of a successful NDA application, Sandoz's Marketing Department designs the "Clozaril patient management system" (CPMS)

1988 Study #30 published in Archives of General Psychiatry

1987 Study #16 published in Journal of Clinical Psychopharmacology

1987 Sandoz submits NDA application for its branded product Clozaril based on studies #30 and #16; the application provides a general overview of CPMS.

1990

1990 Clozapine receives product licence in the UK.

1989 FDA approves NDA; product labeling limits availability of Clozaril to the CPMS [Hurwitz, '01] (September 26)

December 1991 Clozapine is approved for marketing in Canada

1991 The US Senate Subcommittee on Antitrust, Monopolies, and Business Rights convenes a hearing to consider the CPMS bundling issue.

April 1991 Sandoz unbundles CPMS in the U.S., relinquishing control of blood testing and distribution and opening up the clozapine market to standard distribution channels. However, the company maintains a major role in hematological safety by agreeing to run the Clozapine National Non-Rechallenge masterfile. Unbundling lowers U.S. costs of the drug alone to $4160 per patient per year.

1991 Sandoz relinquishes control of blood testing and distribution in April.

1991 In May, the US Senate Subcommittee issues a ruling in support of Sandoz's decision to unbundle CPMS. In addition, it orders that the company settles the class action suit and that state Medicaid programs cover the costs of Clozaril treatment.

1992 Sandoz significantly scales back Clozaril marketing resources 2 years before the end of its 5-year exclusivity period.

1990 In December, 33 states and the District of Columbia bring a class action antitrust law suit against Sandoz in Federal Court.

1990 CLOZ enters US market as bundled product (CPMS) on February 5, as a result of its prohibitive price, neither Medicaid nor private insurance cover the drug.

1994 International Pharmaceutical Abstracts publishes earliest evidence of clozapine's lipid effects.

1994 First report of Clozapine's glucoregulatory effects is published as a Letter to the Editor in American Journal of Psychiatry.

1994

1995 Meltzer and Okayli report in American Journal of Psychiatry that CLOZ appears to be associated with marked reduction in suicidality.

1995 To investigate troubling findings from the FDA Spontaneous Reporting System database, Sandoz sponsors an analysis of its patient registry data [Dubitsky/FDA, '02]. A key finding of this analysis is a markedly reduced risk of suicide in current versus past Clozaril users.

1995 Sandoz submits a supplement to its NDA (sNDA) with the purpose of describing Clozaril's anti-suicidal effects in the product labeling and to request an expansion of the drug's indication. The FDA rejects the application.

1997

1996 Sandoz and Ciba-Geigy merge and become Novartis

1996 Dan Vasella MD, CEO of Novartis, approves funding for an RCT that will assess CLOZ's anti-suicidal effectS (Study ABA 451).

1997 Zenith Goldline Pharmaceuticals (now IVAX Pharmaceuticals) receives FDA approval for a generic version of clozapine, the first in the US, along with its own Clozapine Patient Registry. Even after the end of its patent exclusivity, Novartis remains responsible for setting clozapine safety-related policies.

1998 The U.S. Schizophrenia PORT strongly recommends clozapine for treatment-resistant schizophrenia.

1998 Canadian Psychiatric Association strongly recommends clozapine for treatment-resistant schizophrenia.

1998 First patient enrolls in study ABA 451 (later renamed InterSePT study), a 2-year multicenter and international RCT that compares risk of suicidal behavior among patients on CLOZ vs. Olanzapine (N=980).

2000 The Psychiatrist publishes a study reporting on geographic variation in clozapine prescribing, which may be due to variation in provider adherence to clinical guidelines.

2001

2001. Two studies suggesting that the Zenith/ IVAX generic product may not be bioequivalent to Clozaril lead to a review by the FDA for possible action. While Novartis uses the Ereshefsky study to discourage switches to its generic rival, Zenith/IVAX launches a lawsuit against Novartis and along with the US Generic Pharmaceutical Association attacks the study in press releases, news reports, and letters to the FDA.

2002 Novartis submits an sNDA to the FDA requesting a new indication for Clozaril based on InterSePT results.

2002 FDA approves use of CLOZ for patients at risk for emergent suicidal behavior.

February 2003 Generic clozapine enters Canadian markets following clinical trials in Canada under the regulatory supervision of Health Canada.

2003 National Institute for Clinical Excellence (UK) strongly recommends clozapine for treatment-resistant schizophrenia.

2003 InterSePT study's main finding of a definitive CLOZ advantage is published in Archives of General Psychiatry.

2003 Four to 6 months after gaining FDA approval for Clozaril's suicidality indication, Vasella halts the company's educational/ marketing efforts.

2003 FDA issues a letter asking manufacturers of all atypical antipsychotics to add text to the WARNINGS section of product label stating that epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in atypical-treated patients.

2004

2004 American Psychiatric Association strongly recommends clozapine for treatment-resistant schizophrenia as well as suicidality.

2005 Canadian Psychiatric Association additionally recommends clozapine for suicidality.

2004 The American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists and the North American Association for the Study of Obesity publish a consensus statement on atypical antipsychotics and risk for obesity and diabetes. Its main conclusion is that clozapine and olanzapine have the strongest association with weight gain, diabetes, and dyslipidemia, recommending metabolic baseline screening and monitoring for all patients prescribed atypicals.

2006 McEvoy and colls publish results from phase 2 of the *Clinical Antipsychotic Trials of Intervention Effectiveness* (CATIE), an NIH-funded RCT; they showed that for patients with schizophrenia "who prospectively failed to improve with an atypical antipsychotic (olanzapine, quetiapine, or risperidone), clozapine was more effective than switching to another atypical antipsychotic," and that safety monitoring is necessary to detect and manage clozapine's serious side effects.

March 2005 Psychiatric Services publishes a study showing differences in use rates and dosages of clozapine in populations with similar diagnoses and demographic characteristics residing in the U.S. and Australia.

February 2009 UK's MRHA grants marketing authorization for two generic clozapine products based on bioequivalence study results

2009 Finnish investigators publish results of a large cohort study that concluded that "long-term treatment with antipsychotic drugs is associated with lower mortality compared with no antipsychotic use." They also concluded that atypical drugs are highly heterogeneous, and that clozapine seems to be associated with a substantially lower mortality than all other antipsychotics.

5.9 References

Ackenheil, M., Hippius, H., (1977). 'Clozapine.' In E. Usdin, I.S. Forrest, eds., *Psychotherapeutic Drugs: part II*. New York, Marcel Dekker.

Amsler, H. A., Teerenhovi, L., et al., (1977). 'Agranulocytosis in Patients Treated with Clozapine. A study of the Finnish epidemic.' *Acta Psychiatra Scandinavica* 56(4), 241–248.

Angermeyer, M. C., Löffler, W. et al., (2001). 'Patients' and Relatives' Assessment of Clozapine Treatment.' *Psychological Medicine* 31(03): 509–517.

Angst, J., Bente, P., et al., (1971). *Pharmakopsychiatry* 4, 201.

Angst, J., Jaenicke, A., et al., (1971). *Pharmakopsychiatry* 4, 192.

Anonymous (2004). 'Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes.' *Diabetes Care* 27(2), 596–601.

Balassa, M., Deisenhammer, E. et al., (1971). *Wiener Medizinische Wochenschrift*, 121, 90.

Bastani, B., Alphs, L. D. et al., (1989). 'Development of the Clozaril Patient Management System.' *Psychopharmacology* (Berlin) 99 Suppl, S122–125.

Bente, D., Engelmeier, M. et al. (1967). *Excerpta Medica International Congrgress Series*, 129, 977.

Bindra, J. S. and Lednicer, D. (1982). *Chronicles of Drug Discovery*. New York: John Wiley.

Canadian Psychiatric Association (2005). 'Canadian Clinical Practice Guidelines for the Treatment of Schizophrenia.' *Canadian Journal of Psychiatry*.

Casey/US FDA (1989). Thirteenth Meeting, Psychopharmacologic Drugs Advisory Committee.

Cheng, M. (2009). 'Study: clozapine may have saved schizophrenics.' *Associated Press*.

Claghorn, J., Honigfeld, G. et al., (1987). 'The Risks and Benefits of Clozapine versus Chlorpromazine.' *Journal of Clinical* Psychopharmacoly, 7(6), 377–384.

'Clozapine's Price, and Value'. *The New York Times*, 3 June 1991. As of 25 September 2013: http://www.nytimes.com/1991/06/03/opinion/clozapine-s-price-and-value.html

Clozaril monograph (1991). Novartis Pharmaceuticals Canada Inc.

Conley, R. R., Kelly, D. L., et al. (2005). 'Comparison of Clozapine Use in Maryland and in Victoria, Australia.' *Psychiatric Services*, 56(3), 320–323.

Crilly, J. (2007). 'The History of Clozapine and its Emergence in the US Market.' *History of Psychiatry*, 18(1), 39–60.

Crilly: Personal Communication (2012).

Dubitsky/US FDA (2002). *Clozaril for Suicidality: review and evaluation of clinical data*.

Freudenreich, O., Cather, C., et al., (2004). 'Attitudes of Schizophrenia Outpatients Toward Psychiatric Medications: relationship to clinical variables and insight.' *Journal of Clinical Psychiatry* 65(10), 1372–1376.

Freudhiem, M. (1990). 'Maker of Schizophrenia Drug Bows to Pressure to Cut Cost.' *New York Times*.

Ghaeli, P. (1994). 'Increased serum triglyceride levels in patients treated with clozapine.' *International Pharmaceutical Abstracts*, 31, 2243.

Goleman, D. (1990). 'HEALTH: Outcry Grows Over Method of Selling New Drug.' *New York Times*.

Goodman, C., Ahn, R., et al., (1990). *Market Barriers to the Development of Pharmacotherapies for the Treatment of Cocaine Abuse and Addiction: Final Report*, Lewin Group.

Grace, J. J. and Szarowicz, R. S., (2001). 'The Clozapine Access Project.' *Psychiatric Services* 52(1), 108–a.

Greenhalgh, T., Robert, G., et al., (2004). 'Diffusion of Innovations in Service Organizations: systematic review and recommendations.' *The Milbank Quarterly* 82(4), 581–629.

Gross, H. and Langner, E., (1966). 'Das Wirkungsprofil eines chemisch neuartigen Breitbandneuroleptikums der Dibenzodiazepingruppe.' *Wiener Medizinische Wochenschrift* 116, 814–816.

Hayhurst, K. P., Brown, P., et al., (2003). 'Postcode Prescribing for Schizophrenia.' *The British Journal of Psychiatry* 182(4), 281–283.

Hemphill, R. E., Pascoe, F. D., et al., (1975). 'An Investigation of Clozapine in the Treatment of Acute and Chronic Schizophrenia and Gross Behaviour Disorders.' *South African Medical Journal* 49(51), 2121–2125.

Hippius, H. (1999). 'A Historical Perspective of Clozapine.' *Journal of Clinical Psychiatry* 60, Suppl. 12, 22–23.

Hippius, H. and G. Stille (1973). 'Zur küftigen Entwicklung der Neuroleptika.' De La Fuente B., Weisman M.N. eds. Psychiatry. *Proceedings of the 5th World Congress of Psychiatry*, Mexico, D.F., 25 Nov – 4 Dec 1971, Part 1, Symp. 8. Excerpta Medica Amsterdam, 571–575.

Honigfeld, G., Arellano, F., et al., (1998). 'Reducing Clozapine-related Morbidity and Mortality: 5 years of experience with the Clozaril National Registry.' *Journal of Clinical Psychiatry* 59, 3–7.

Honigfeld/US FDA (1989). Thirteenth Meeting, Psychopharmacologic Drugs Advisory Committee.

Honigfeld: Personal Communication (2011).

Hurwitz, M. A. (1992). 'Bundling Patented Srugs and Medical Services: an antitrust analysis.' *Speciality Law Digest Health Care Law* 155, 7–39.

Idanpaan-Heikkila, J., Alhava, E., et al., (1975). 'Letter: clozapine and agranulocytosis.' *Lancet* 2(7935), 611.

Idanpaan-Heikkila, J., Alhava, E., et al., (1977). 'Agranulocytosis During Treatment with Chlozapine.' *European Journal of Clinical Pharmacology* 11(3), 193–198.

Kamran, A., Doraiswamy, P. M., et al. (1994). 'Severe Hyperglycemia Associated with High Doses of Clozapine.' *American Journal of Psychiatry* 151(9), 1395.

Kane, J., Honigfeld, G., et al., (1988). 'Clozapine for the Treatment-Resistant Schizophrenic: a double-blind comparison With chlorpromazine.' *Archives of General Psychiatry* 45(9), 789–796.

Kane, J. M., Marder, S. R., et al., (2001). 'Clozapine and Haloperidol in Moderately Refractory Schizophrenia: a 6-Month randomized and double-blind comparison.' *Archives of General Psychiatry* 58(10), 965–972.

Kane: Personal Communication (2012).

Leber/US FDA (1989). Thirteenth Meeting, Psychopharmacologic Drugs Advisory Committee.

Leber: Personal Communication (2012).

Lehman, A. F., Lieberman, J. A., et al., (2004). 'Practice Guideline for the Treatment of Patients with Schizophrenia.' Second edition. *American Journal of Psychiatry* 161, Suppl. 2, 1–56.

Leslie, D. and Rosenheck, R. A., (2005). *Seventh Annual Report on Pharmacotherapy of Schizophrenia in the Department of Veterans Affairs*. West Haven, CT, Northeast Program Evaluation Center.

McEvoy, J. P., Lieberman, J. A., et al., (2006). 'Effectiveness of Clozapine Versus Olanzapine, Quetiapine, and Risperidone in Patients With Chronic Schizophrenia Who Did Not Respond to Prior Atypical Antipsychotic Treatment.' *American Journal of Psychiatry* 163(4), 600–610.

Meltzer, H. (2005). 'Suicide in Schizophrenia, Clozapine, and Adoption of Evidence-based Medicine.' *Journal of Clinical Psychiatry* 66(4), 530–538.

Meltzer, H. Y., Alphs, L., et al., (2003). 'Clozapine Treatment for Suicidality in Schizophrenia: International Suicide Prevention Trial (InterSePT).' *Archives of General Psychiatry* 60(1), 82–91.

Meltzer, H. Y. and Fatemi, H., (1995). 'Suicide in Schizophrenia: the effect of clozapine.' *Clinical Neuropharmacology* 18, S18–S24.

Meltzer, H. Y., Goode, D. J., et al., (1979). 'Effect of Clozapine on Human Serum Prolactin Levels.' *American Journal of Psychiatry* 136(12): 1550–1555.

Meltzer, H. Y. and Luchins, D. J., (1984). 'Effect of Clozapine in Severe Tardive Dyskinesia: a case report.' *Journal of Clinical Psychopharmacology* 4(5), 286–287.

Meltzer, H. Y., Matsubara, S., et al., (1989). 'Classification of Typical and Atypical Antipsychotic Drugs on the Basis of Dopamine D-1, D-2 and Serotonin2 pKi values.' *Journal of Pharmacology and Experimental Therapeutics* 251(1), 238–246.

Meltzer, H. Y. and Okayli, G., (1995). 'Reduction of Suicidality During Clozapine Treatment of Neuroleptic-resistant Schizophrenia: impact on risk-benefit assessment.' *American Journal of Psychiatry* 152, 183–190.

Meltzer: Personal Communication (2012).

Metzenbaum, H. (1991). *Marketing of Clozaril: improved safety or barrier to access*. Washington, DC, Subcommittee on Antitrust, Monopolies, and Business Rights.

National Institute for Clinical Excellence (2003). 'The NICE Guideline on Core Interventions in the Treatment of Schizophrenia in Adults in Primary and Secondary Care.'

Purcell, H. and Lewis, S., (2000). 'Postcode Prescribing in pPsychiatry: clozapine in an english county.' *Psychiatric Bulletin* 24(11), 420–422.

Schmutz, J. and Eichenberger, E., (1982). 'Clozapine' in *Chronicles of Drug Discovery* 1, 39–59.

Sernyak, M. J. and Rosenheck, R. A., (2008). 'Antipsychotic Use in the Treatment of Outpatients with Schizophrenia in the VA from Fiscal Years 1999 to 2006.' *Psychiatric Services* 59(5), 567–569.

Sherman, C., (2005). 'Necessity drives schizophrenia polypharmacy.' *Clinical Psychiatry News* 33.

Shopsin, B., Klein, H., et al., (1979). 'Clozapine, Chlorpromazine, and Placebo in Newly Hospitalized, Acutely Schizophrenic Patients: a controlled, double-blind comparison.' *Archives of General Psychiatry* 36(6), 657–664.

Stille, G. and Hippius, H., (1971). 'Kritische Stellungsnahme zum Begriff der Neuroleptika (anhand von pharmakologischen und klinischen Befunden mit Clozapin).' *Pharmakopsychiatrie Neuro-Psychopharmakologie* 4, 182–191.

Stroup, T. S., McEvoy, J. P., et al., (2004). 'Revised PORT Recommendations.' *Schizophrenia Bulletin* 30(3), 609–611.

Tamminga, C. A. (2006). 'Practical Treatment Information for Schizophrenia.' *American Journal of Psychiatry*, 163(4), 563–565.

Tiihonen, J., Lonnqvist, J., et al., (2009). '11-year Follow-up of Mortality in Patients with Schizophrenia: a population-based cohort study (FIN11 study).' *Lancet* 374(9690), 620–627.

Tokarski, C. (1990). 'Sandoz Pressured to Make Drug Accessible.' *Modern Healthcare* 20(37), 39.

Tomlinson: Personal Communication (2011). MHRA.

US FDA (2002). Final Minutes, Psychopharmacologic Drugs Advisory Committee.

Walker, A. M., Lanza, L. L., et al., (1997). 'Mortality in Current and Former Users of Clozapine.' *Epidemiology* 8(6), 671.

CHAPTER 6 Addressing the metabolic side effects of second-generation antipsychotics

6.1 Summary

Until clozapine, the first second-generation antipsychotic (SGA), became more widely available in the early 1990s, the only medications for the treatment of psychotic symptoms in people with schizophrenia were agents now known as first-generation antipsychotics (FGAs). Whilst early research did appear to associate FGAs with metabolic dysregulation, attention shifted away from this with the increased use of compounds with a higher risk of neurological side effects. Clozapine's metabolic effects garnered some attention, but clinical and pharmaco-epidemiological research aimed at clarifying the association between SGA use and metabolic dysregulation only began in earnest after olanzapine, risperidone, and quetiapine entered the market. These SGAs not only displaced FGAs for the treatment of schizophrenia, but they also began to be used for additional conditions, many of them off-label, thus dramatically expanding the population exposed to their adverse effects. Multiple case reports and small case series suggesting an association between SGA use and metabolic dysregulation were published in the 1990s and early 2000s. These studies proved to be extremely valuable harbingers of the firmer randomised and meta-analytic evidence that, with the exception of a 1999 meta-analysis focused on the drugs' weight effects, were published in the mid and late 2000s. In addition to the aforementioned meta-analysis, critical contributions to the empirical evidence were a series of studies based on analyses of a database maintained by the US Food and Drug Administration (FDA) containing adverse events voluntarily reported to the agency, and a study conducted by Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) investigators focused on prospectively assessed metabolic effects of the antipsychotics used in the trial.

The earliest organised response to the emerging empirical evidence occurred in 2001 when researchers attending the Mount Sinai Conference in the US addressed the question of what the focus of clinician monitoring when prescribing SGAs should be, and how that information should influence practice. The question was taken up at a follow-up meeting, the sole objective of which was to develop recommendations for the health monitoring of patients with schizophrenia on antipsychotic treatment.

Regulators around the world also took notice. In 2002, the UK's Committee on Safety of Medicines and the Medicines Control Agency recommended glucose monitoring in patients at risk for diabetes, and the Japanese regulator ordered a label warning for olanzapine on its risk for serious hyperglycemia, also calling for glucose monitoring. In

2003, the FDA issued a class warning on the increased risk of treatment-emergent hyperglycemia and related adverse events associated with SGA use. Later that year, the American Diabetes Association (ADA), the American Psychiatric Association (APA), and other professional organisations met to discuss the metabolic side effects of SGAs. The consensus statement that emerged from that conference, simultaneously published in two journals in early 2004, ranked antipsychotics on their degree of metabolic risk and recommended metabolic screening and monitoring of patients prescribed SGAs. In 2004, two major US organisations published guidelines with monitoring recommendations; the UK's main guideline developer – the National Institute of Clinical Excellence (NICE) – published its updated Clinical Guideline on Schizophrenia with monitoring recommendations in 2010.

The earliest of a series of lawsuits filed against Eli Lilly, AstraZeneca, and Pfizer for their handling of safety information or illegal promotional activities burst onto the public scene in June 2005, when Lilly agreed to pay $690 million to settle liability claims based on allegations that Zyprexa (branded olanzapine) caused hyperglycemia-related side effects. Other legal developments followed, the latest of which was a $198 million settlement by Astrazeneca in connection with side effects from Seroquel (branded quetiapine).

Despite the empirical evidence, regulators' warnings, and clinical guidelines, studies have found generally low rates of metabolic monitoring in routine practice. In 2008, a US organisation representing the leadership of states' public mental health service systems stated that 'despite having been available for four years, (the) ADA/APA guidelines are generally not followed' (NASMHPD, 2008). A meta-analysis of 48 studies conducted between 2000 and 2011 in the UK, US and other industrialised countries confirmed that observation (Mitchell et al., 2012).

6.2 Case Study Scope

This case study examines the recognition of lipid and glucose dysregulation as well as weight gain as *metabolic side effects* of SGAs. Secondarily, the case study examines recommended and actual changes in the implementation of antipsychotic treatment adopted in response to metabolic side effects. We use the term *glucose dysregulation* to refer to clinically significant hyperglycemia, exacerbation of pre-existing Type 1 and Type 2 diabetes, new-onset Type 2 diabetes mellitus, and diabetic ketoacidosis. Although these conditions may be associated with other abnormalities, key glucoregulatory abnormalities are increased glucose levels which if sustained, lead to increased levels of hemoglobin A1c. We use the term *lipid dysregulation* to refer to clinically significant increases in serum triglycerides or selected cholesterol indices (total cholesterol, low-density lipoproteins [LDL]), or decreases in high-density lipoprotein [HDL] concentrations. We note that empirical evidence of a causal association between SGA use and diabetes mellitus is less robust than for other glucoregulatory abnormalities. We further note that like others, we focus on weight gain as an easier-to-assess proxy for increases in central adiposity, the underlying metabolic phenomenon.

6.3 Glossary

Akathisia: a condition marked by restlessness and inability to sleep or relax that may be observed with antipsychotic drug treatment.

Antipsychotic drugs: medications used to control psychotic symptoms. Two classes of antipsychotic drugs exist: first-generation (or conventional) and second-generation (or atypical). This classification is based on their mechanism of action. However, while all first-generation antipsychotics were developed between the 1950s and the 1980s, all second-generation antipsychotics, with the exception of clozapine, which was developed in 1959, were developed since the 1990s. FGAs may be further classified as low-, medium- or high-potency, depending on the dosage needed to achieve therapeutic effects. Chlorpromazine is a low-potency FGA.

Extrapyramidal Symptoms: involuntary movements reflecting abnormal extrapyramidal function that may be observed with antipsychotic drug treatment. These include acute dystonic reactions, parkinsonism and akathisia.

Glycosuria: glucose in the urine.

Hypertriglyceridemia: increased levels of triglycerides.

Hyperprolactinemia: increased levels of prolactin, a hormone produced by the *pituitary* gland.

Off-label: the use of medication for unapproved conditions or patient groups, or in unapproved dosages.

Phenothiazine antipsychotic: largest chemical class of first generation antipsychotics that includes chlorpromazine among others.

Plasma: a component of blood accounting for more than half of its volume.

QTc: in the electrocardiogram (EKG), the interval representing the time for both ventricular depolarisation and repolarisation to occur, corrected so that it is not affected by the person's heart rate. Complications of QTc prolongation include arrhythmias that although rare, may be life threatening.

Serum: plasma free of blood clotting factors.

Tardive Dyskinesia: neurological disorder resulting in involuntary, repetitive body movements that may result from prolonged antipsychotic drug treatment.

6.4 Acronyms

ADA: American Diabetes Association

AHRQ: Agency for Healthcare Research and Quality

APA: American Psychiatric Association

BMI: body mass index

CATIE: Clinical Antipsychotic Trials of Intervention Effectiveness

EKG: electrocardiogram

FDA: US Food and Drug Administration

FGA: first-generation antipsychotic

MS: metabolic syndrome

NASMHPD: National Association of State Mental Health Program Directors

NIMH: National Institute of Mental Health

PORT: Patient Outcomes Research Team

SGA: second-generation antipsychotic

DTCA: direct-to-consumer advertising

6.5 Timeline of key events

Key:

UK
US
Other international development (Europe, Japan)

Year	Event
November 1952	Chlorpromazine enters the market (France)
1954	Three years before gaining US Food and Drug Administration (FDA) approval, chlorpromazine, the first antipsychotic and a phenothiazine compound, enters US market for the treatment of psychotic symptoms.
1956	Journal of the American Medical Association (JAMA) publishes a paper providing earliest evidence of an association between chlorpromazine and glucoregulatory abnormalities (Hiles 1956). The authors reported on five patients in a large psychiatric hospital who developed transient hyperglycemia and glycosuria.
1957	A second antipsychotic (perphenazine), also a phenothiazine, enters the US market after gaining approval from the US FDA.
1958	Journal of Nervous & Mental Diseases publishes a paper providing earliest evidence of an association between chlorpromazine and lipid abnormalities (Mefferd, Labrosse, Gawienowski, & Williams 1958). Chlorpromazine was shown to increase cholesterol levels in people with chronic schizophrenia.
1964	American Journal of Psychiatry publishes earliest evidence of an association between chlorpromazine and weight gain (Winkelman 1964). Two hundred patients treated with chlorpromazine were followed over 10.5 years. The authors found that tolerance developed

	early to all side effects except for weight gain.
Early 1970s	Clozapine, the first atypical or second generation antipsychotic (SGA), enters several European and other world markets, available in the US experimentally only.
November 1975	South African Medical Journal publishes earliest evidence of an association between clozapine and weight gain (Hemphill, Pascoe, & Zabow 1975). The authors found that clozapine-treated patients had an average weight gain of 1kg/week during the six-week study.
May 1984	Atherosclerosis publishes a study by Japanese researchers showing that phenothiazine antipsychotics are associated with increases in triglyceride levels and low-density lipoproteins, and with decreased high-density lipoprotein concentrations (Sasaki, Kumagae, Sata, Kuramitsu, & Arakawa 1984). The first author published another study on the same topic the following year (Sasaki, Funakoshi, & Arakawa 1985).
September 1985	The US FDA removes a voluntary moratorium on advertising directly to consumers, stating that existing regulations governing marketing directed toward physicians were 'also sufficient to protect consumers' (Calfee 2002).
1985	The US FDA includes provisions allowing for evidence generated from non-inferiority trials to be used in the drug approval process (US Government Accountability Office 2010).
March 1986	Hospital & Community Psychiatry publishes a study showing high prevalence of chronic medical illness among chronic mentally ill patients (McCarrick, Manderscheid, Bertolucci, Goldman, & Tessler 1986).
January 1990	Clozapine receives product licence in the UK
February 1990	Clozapine, the first atypical or second generation antipsychotic (SGA) enters the US market a little over four months after receiving approval for marketing by the US FDA for treatment-refractory symptoms of schizophrenia.
April 1990	American Journal of Psychiatry publishes a study reporting on the experience of 6/7 patients on clozapine who gained 6-69 pounds (Cohen, Chiles, & MacNaughton 1990). The authors wrote 'Because of clozapine's anticipated availability in the US, clinicians should be aware of this possible side effect, which, to the authors' knowledge, has not been reported previously.'
December 1993	Risperidone, the second commercially available SGA in the US, is approved for marketing by the US FDA for manifestations of psychotic disorders.

September 1994	American Journal of Psychiatry publishes a paper providing earliest evidence of the glucoregulatory effects of clozapine (Johnsen & Jorgensen 2008). The authors reported on a case of 'severe, sustained glycemia' in a patient with no prior history of diabetes or glucose intolerance, who had been treated with clozapine for two months.
September 1994	International Pharmaceutical Abstracts publishes an abstract entitled 'Increased serum triglyceride levels in patients treated with clozapine', providing the earliest evidence of an association between clozapine and lipid dysregulation (Ghaeli 1994).
September 1996	Olanzapine, the third commercially available SGA in the US, is approved for marketing by the US FDA; it will go on to dominate the US antipsychotic market for the next decade.
April 1997	American Journal of Psychiatry publishes results of an Eli Lilly-funded randomised controlled trial (RCT) comparing olanzapine to haloperidol (Tollefson et al. 1997). In addition to efficacy results, authors report that olanzapine had a 'substantially more favourable safety profile' than haloperidol.
August 1997	The US FDA issues a 'Guidance for Industry Direct-to-Consumer Prescription Drug Promotion' stating that only broadcast advertisements on television or radio were subjected to the requirement to describe risks and side effects (US Government Accountability Office 2002).
September 1997	Quetiapine, the fourth commercially available SGA in the US, is approved for marketing by the US FDA for the management of manifestations of psychotic disorders.
February 1998	The New York Times publishes a piece entitled 'Psychiatric Drugs Are Now Promoted Directly to Patients' (Freudenheim 1998). The article describes the explosive growth of direct-to-consumer advertising (DTCA) of prescription drugs and states 'patients who are influenced by the marketing programs may seek out doctors who might be willing to prescribe drugs that are not right for them'.
October 1998	Biological Psychiatry publishes a case series suggesting that in addition to clozapine, olanzapine is also associated with new onset diabetes (Wirshing, Spellberg, Erhart, Marder, & Wirshing 1998). Six new cases of clozapine- and olanzapine-associated diabetes were documented. In addition, four of the six patients experienced substantial weight gain.
August 1999	Journal of Clinical Psychiatry publishes first evidence of quetiapine's glucoregulatory effects (Sobel, Jaggers, & Franz 1999). The authors reported on a patient who developed transient diabetes during quetiapine treatment, stating that although they could not establish a causal association, they were 'reasonably sure that other explanations

	were ruled out'.
September 1999	Pharmacotherapy publishes a report describing the reduction in serum triglyceride levels exhibited by four patients with psychotic disorders who were switched from clozapine to risperidone (Ghaeli & Dufresne 1999). The authors recommended monitoring of triglyceride levels in patients receiving clozapine who have other cardiac risk factors.
September 1999	American Journal of Psychiatry publishes earliest evidence of an association between olanzapine and lipid abnormalities (Sheitman, Bird, Binz, Akinli, & Sanchez 1999). Authors recommended monitoring lipid profiles.
November 1999	American Journal of Psychiatry publishes a comprehensive meta-analysis of the evidence on the weight effects of SGAs and the older antipsychotics (Allison et al., 1999). The authors reported that among SGAs, clozapine followed closely by olanzapine, was associated with the largest weight increases.
February 2001	Ziprasidone, the fifth commercially available SGA in the US, is approved for marketing by the US FDA for the treatment of schizophrenia.
February 2001	Two days after ziprasidone's approval, Eli Lilly officials express intense concern with its potential for undermining olanzapine's market dominance (Powell 2001).
March 2001	Medical Care publishes a study on off-label use of antipsychotics among patients treated by the US Veterans Administration in 1999 (Rosenheck 2001). The authors found that 42.8% of patients had off-label use of antipsychotics.
November 2001	JAMA publishes an analysis of cases of newly diagnosed hyperglycemia and exacerbation of preexisting diabetes among children taking clozapine or olanzapine spontaneously reported to the FDA's MedWatch Drug Surveillance System (E. Koller, Malozowski, & Doraiswamy 2001). The authors concluded that the risk of hyperglycemia was higher among patients taking clozapine and possibly also among those taking olanzapine.
December 2001	Journal of Clinical Psychopharmacology reports on 14 cases of severe hypertriglyceridemia associated with olanzapine and quetiapine therapy (Meyer 2001). Authors called for monitoring of serum lipids stating that lipid abnormalities should be added to the concerns about the metabolic consequences of therapy with certain newer antipsychotic agents.
February 2002	Kaiser Family Foundation publishes a study entitled 'Trends in Direct-to-Consumer Advertising of Prescription Drugs' in the US (Frank, Berndt, Donohue, Epstein, & Rosenthal 2002). The authors

	found that DTCA spending grew nine-fold between 1994 and 2000, and that zyprexa (branded olanzapine) and risperdal (branded risperidone) were among the top 20 sellers.
April 2002	Several reports of hyperglycemia and diabetes in patients taking olanzapine cause the UK's Committee on Safety of Medicines and the Medicines Control Agency to recommend appropriate clinical and blood glucose monitoring among patients with risk factors for diabetes mellitus (MHRA 2002).
April 2002	The Pharmaceutical & Food Safety Bureau of the Japanese Ministry of Health, Labour and Welfare orders a label warning for the risk of serious hyperglycemia and calls for careful follow-up procedures during olanzapine administration (Safety Div./MHLW 2002).
July 2002	Pharmacotherapy publishes a study that analysed cases of treatment-emergent diabetes spontaneously reported to the FDA's MedWatch Drug Surveillance System (E. A. Koller & Doraiswamy 2002). The authors reported on serious adverse effects, including deaths, and concluded that the evidence suggested that olanzapine may unmask diabetes in susceptible patients. In a press release that preceded this publication, co-author Doraiswamy stated 'while our report does not prove a causal relationship between [olanzapine] and diabetes, doctors should be aware of such potentially adverse effects…We've found cases where patients had some very serious problems associated with olanzapine, and at least 23 of them died' (Health News Digest 2002).
November 2002	Aripiprazole, the sixth commercially available SGA in the US, is approved for marketing by the US FDA for the treatment of schizophrenia.
February 2003	American Journal of Psychiatry publishes the first RCT that compared the glucoregulatory and lipid effects of three SGAs (clozapine, olanzapine, risperidone) and haloperidol (Lindenmayer et al. 2003). The authors found that clozapine and olanzapine were associated with increases in glucose and cholesterol, and with weight gain. The other drugs had lower risks.
April 2003	The Wall Street Journal publishes an article reporting on new evidence suggesting that olanzapine is associated with new onset diabetes, excess mortality, and dramatic weight gain (WSJ 2003). The newspaper piece was based on the Koller and Doraiswamy study published in July 2002 (E. A. Koller & Doraiswamy 2002).
August 2003	The New York Times reports on preliminary results of a study showing that three SGAs (olanzapine, risperidone, and quetiapine) had a higher risk of diabetes relative to FGAs (Goode 2003). A final version of the study is published in 2006 (Lambert, Cunningham, Miller, Dalack, & Hur 2006).

September 2003	The US FDA requires that SGA manufacturers add text to the 'warnings' section of the product label stating that epidemiological studies 'suggest an increased risk of treatment-emergent hyperglycemia-related adverse events' in SGA-treated patients.
February 2004	Diabetes Care publishes a consensus statement recommending metabolic screening and monitoring for patients prescribed SGAs. The statement is the result of a consensus development conference, attended by representatives from the American Diabetes Association, American Psychiatric Association, the US FDA and the pharmaceutical industry, among others (Anonymous 2004). This report was considered of such importance that it was simultaneously published in two journals (Meyer: Personal Communication 2012).
February 2004	The American Psychiatric Association (APA) publishes the Clinical Practice Guideline for the Treatment of Patients with Schizophrenia, Second Edition, which recommends regular assessment of weight/ body mass index (BMI), glucose and lipid tests (Lehman et al. 2004). The Guideline Watch released five years later makes the same recommendations (Dixon, Perkins, & Calmes 2009).
April 2004	British Journal of Psychiatry publishes a study funded by Eli Lilly reporting that there is no difference in the incidence of glycemic (glucoregulatory) abnormalities between placebo- and antipsychotic-treated subjects or between the study SGAs (Bushe 2004). The authors concluded that 'diabetogenic potential ascribed to SGAs, resulting from retrospective studies, may be incorrect'.
August 2004	American Journal of Psychiatry publishes a paper containing recommendations 'for the systematic health monitoring of individuals with schizophrenia for whom antipsychotic medication is prescribed' (Marder et al. 2004).
2004	The US Veterans Administration (VA) & Department of Defense (DoD) publish the Clinical Practice Guideline for Psychosis which recommends assessment of weight, glucose and lipid tests every 6-12 months during long-term therapy (US VA/DoD 2004).
January 2005	Archives of General Psychiatry publishes a paper authored by Massachusetts General Hospital researchers, including diabetes, obesity, and endocrinology experts reporting on a study that found a higher risk of glucose dysregulation in patients treated with clozapine and olanzapine than those treated with risperidone (Henderson et al. 2005).
June 2005	Lilly agrees to pay $690 million to settle liability claims filed by 8,000 plaintiffs based on allegations that zyprexa (branded olanzapine) caused glucoregulatory side effects (hyperglycemia and diabetes). Lilly pays another $500 million to settle 18,000 more law suits (Berenson

	2007).
September 2005	New England Journal of Medicine (NEJM) publishes results from Phase I of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) comparing four SGAs (olanzapine, quetiapine, risperidone, and ziprasidone) and perphenazine. Results showed that although olanzapine was the most effective in terms of rates of discontinuation, it was 'associated with greater weight gain and increases in measures of glucose and lipid metabolism' (Lieberman et al. 2005).
2005	The journal CNS Drugs publishes a comprehensive literature review focused on the association between eight SGAs available in the US and/or Europe, and weight gain and glucose and lipid dysregulation (Newcomer 2005). The author concludes that based on RCT evidence, 'weight gain liability varies significantly across' the SGAs, with clozapine and olanzapine posing the greatest risk of clinically significant weight gain. Based on evidence of variable quality, the author concluded that SGAs 'are associated with differing effects on glucose and lipid metabolism,' with clozapine and olanzapine posing 'an increased risk of diabetes mellitus and dyslipidaemia.'
June 2006	The APA Clinical Practice Guideline on Psychiatric Evaluation of Adults, Second Edition, recommends that psychiatric evaluations include baseline and follow-up assessment of glucose and lipid levels to identify SGA effects (APA 2006).
December 2006	Bristol-Myers Squibb agrees to pay more than $515 million to settle civil lawsuits for alleged fraudulent marketing of abilify (branded aripiprazole) for off-label uses (US DoJ 2007).
May 2007	Schizophrenia Bulletin publishes a study of UK SGA users which found annual assessment of blood pressure in 26% of patients, weight in 17%, glucose parameters in 28% and serum lipids in 22%, with all four measures documented in 11% (Barnes, Paton, Cavanagh, Hancock, & Taylor 2007).
June 2007	Lilly settles 900 additional class action lawsuits in connection with zyprexa product liability (CCHR 2009).
February 2008	Schizophrenia Research publishes a study by CATIE investigators reporting on antipsychotic-related changes in metabolic parameters among CATIE subjects. Among other findings, authors found that olanzapine was associated with the largest increase in waist circumference, followed by quetiapine, whereas no change was evident for ziprasidone. While metabolic syndrome status increased for olanzapine, it decreased for ziprasidone (Meyer et al. 2008).
May 2008	Psychiatric Services publishes a study that found that, between 1996/97 and 2004/05 in the US, the prevalence of SGA use increased

	almost seven-fold, whereas FGA use dropped four-fold (Domino & Swartz 2008).
October 2008	An investigation of Lilly filed by 33 states in the US ends in an injunction calling Lilly to pay $52 million as well as conform to restrictions and reforms regarding marketing and promotion of zyprexa (US DoJ 2009a).
January 2009	Lilly pleads guilty to criminal charges of unlawful promotion of zyprexa and pays $515 million in fines, in addition to $800 million for the settlement of a federal civil investigation (US DoJ 2009a).
February 2009	Diabetes Care publishes a study of SGA users in a US commercial health plan, which found annual assessment rates of 38% and 23% for glucose and lipid tests, respectively, during the period 2001-2006 (Morrato et al. 2009).
September 2009	The US Department of Justice orders Pfizer to pay $2.3 billion in criminal and civil fines for illegal promotion of its products, including geodon (branded ziprasidone) (Barrett 2009; US DoJ 2009b).
October 2009	JAMA publishes results of a cohort study showing significant cardiometabolic risk for first-time use of SGAs in children and adolescents (Correll et al. 2009). This study is the focus of two newspaper pieces published the same year (Rockoff 2009; Wilson 2009).
April 2010	The UK's National Institute for Health and Clinical Excellence (NICE) Updated Clinical Guideline on Schizophrenia recommends that first-line healthcare professionals monitor physical health of schizophrenia patients at least once a year, with a focus of cardiovascular disease risk assessment and diabetes (NICE, 2010).
April 2010	Astrazeneca agrees to pay $520 million to settle a probe by the US Attorney's Office in Philadelphia over allegations of illegal promotion of seroquel (branded quetiapine). The company also paid around $198 million to settle cases brought by patients claiming side effects from seroquel (US DoJ 2010).
October 2010	Journal for Healthcare Quality publishes the results of a national evaluation of VA mental health services which found that, during the one-year study period, 85% and 78% of patients had glucose and lipid tests, respectively (Watkins et al. 2010).
July 2011	British Journal of Psychiatry publishes a study by Irish investigators which found that the majority of general practitioners are willing to perform medical management of metabolic dysregulation emerging from antipsychotic treatment prescribed by specialists (Bainbridge, Gallagher, McDonald, McDonald, & Ahmed 2011).
August 2011	British Journal of Psychiatry publishes a study that evaluated the

	content and quality of screening guidelines for cardiovascular risk in schizophrenia and found that four out of the 18 guidelines evaluated were of good quality (De Hert et al. 2011).
January 2012	Psychological Medicine publishes a meta-analysis that showed low rates of metabolic monitoring in patients prescribed antipsychotic drugs (Mitchell, Delaffon, Vancampfort, Correll, & De Hert 2012).

6.6 Narrative

Studies conducted in the pre-antipsychotic era suggested that schizophrenia confers a higher risk for glucoregulatory abnormalities (Kooy, 1919; Raphael and Parsons, 1921). However, the evidence for a true association is weak (Newcomer May, 2011), and findings from a study specifically designed to investigate this association ruled out a preexisting impairment of glucose metabolism in never-medicated first-episode schizophrenic patients (Arranz, Rosel et al., 2004).

Chlorpromazine, a phenothiazine drug and the first antipsychotic agent, was synthesised in December 1950 in the laboratories of Rhône-Poulenc (France), in the context of research on antihistaminic substances after World War II, and initially used as an anesthetic (Lopez-Munoz, Alamo et al. 2005).The potential use of chlorpromazine in psychiatry was first recognised by Henri Laborit: he employed the drug as an adjunct to surgical anesthetics and found that it caused disinterest and with only a slight tendency to sleep (Ban 2007). Soon after entering the French market in November 1952, the drug became available in many other countries. Evidence of its metabolic side effects in humans first surfaced not long after the drug entered the US market in 1954. The earliest evidence of an association between chlorpromazine and glucose dysregulation – a report of five hospitalized patients who developed transient hyperglycemia and glycosuria – was published in 1956 (Hiles 1956). The earliest evidence of an association between chlorpromazine and lipid dysregulation was published in 1958, with a study reporting that chlorpromazine-treated patients exhibited increases in triglyceride and to a lesser extent, total cholesterol levels (Mefferd, Labrosse et al. 1958). A study published in 1960 replicated those findings (Clark ML 1960). A large study that followed chlorpromazine-treated patients for over ten years was the first to report on an association between chlorpromazine and weight gain (Winkelman 1964). A handful of studies pointed to an increased risk of glucoregulatory abnormalities in patients receiving chlorpromazine and other phenothiazine *first-generation antipsychotics* (FGAs) (Jori, Bernardi et al. 1964; Schwarz L 1968; Thonnard-Neumann 1968).

Several higher-potency FGAs introduced in the late 1950s eroded market share for chlorpromazine (a low-potency FGA), and with the arrival of haloperidol in the late 1960s, chlorpromazine became a second-line drug in most Western markets. Reports of neurological symptoms including extrapyramidal symptoms and tardive dyskinesia associated with high potency antipsychotics began surfacing in the early 1960s (Ayd 1961; Faurbye and Clausen 1964). By the late 1960s, the psychiatric field had decidedly embraced these side effects as the most important focus of their safety concerns regarding antipsychotic drug treatment (Haupt and Newcomer 2001). Perhaps as a result of this

shift, attention to antipsychotics' metabolic effects – measured in the number of studies dedicated to the topic – waned after the 1970s. An exception to this trend was research conducted in Japan and published in the mid 1980s suggesting that unlike higher potency FGAs, phenothiazine FGAs were associated with increases in triglyceride levels and low-density lipoproteins and with decreased high-density lipoprotein concentrations (Sasaki, Kumagae et al. 1984; Sasaki, Funakoshi et al. 1985). Psychiatry's intense focus on the neurological side effects of FGAs may have positively predisposed the field toward drugs that, like most of the *second-generation antipsychotics* (SGAs), had notably lower rates of such side effects (Meyer: Personal Communication 2012).

The first study suggesting that SGAs may also be associated with metabolic side effects was an observational study conducted by South African researchers and published in 1975 that found significant weight gain among patients treated with clozapine (Hemphill, Pascoe et al. 1975). Clozapine, the first SGA, was commercially available in Europe and other parts of the world for a good part of the early 1970s. In the 1980s, German researchers reported on hypertriglyceridemia associated with fluperlapine, an experimental SGA structurally related to clozapine (Muller-Oerlinghausen 1984; Fleischhacker, Stuppack et al. 1986) .

Two important regulatory developments occurred in 1985 in the US. In September that year, the US *Food and Drug Administration* (FDA) removed a voluntary moratorium on advertising directly to consumers, stating that existing regulations governing marketing directed toward physicians were 'also sufficient to protect consumers;' the agency, however, required that all advertisements include a complete description of risks and side effects (FDA 1995). Following this decision, pharmaceutical companies began promoting drug products directly to patients, a practice known as *direct-to-consumer advertising* (DTCA). As research would later demonstrate, SGAs were among the drugs most heavily advertised to the public under this new provision. The FDA also ruled in 1985 that evidence generated from *non-inferiority* (NI) trials could be used in the drug approval process. Regulations established that for a NI trial to be interpretable, it was critical to demonstrate that the active control had an expected effect, typically done by including a placebo arm in the trial (FDA 2010; GAO 2010; Taylor 2010) (Potter: Personal Communication 2012). NI comparisons are mainly done to show that a new compound which separates from placebo is not inferior in terms of efficacy to a currently marketed compound. William Z. Potter, MD, PhD, formerly head of early CNS clinical development at Eli Lilly from 1996–2004, believes that the relative ease of meeting NI criteria subtly works against the field investing in better ways to demonstrate superiority of one compound over another in the complex realm of clinical efficacy. For the last two decades, the development focus for new antipsychotics has been on demonstrating 'superiority' in the side effect realm on simple and easily quantifiable measures as weight gain or serum prolactin. He argues that using current NI criteria, true differences in aspects of efficacy could easily be missed with the trial designs, clinical populations and approaches to running studies on which industry depends to bring agents to the market. Furthermore, given the longer clinical developmental timelines at substantially higher costs to adequately assess superiority, under current patent law there is little incentive for a company to pursue such a claim. It is likely that the company who identified the pharmacologic mechanism associated with superior efficacy would have taken so long to establish the finding that a competitor could much more quickly bring forward an equally effective compound that avoided some of the side

effects usually associated with any 'first in class' CNS compound. In his view, a well-meaning patent law inadvertently favored 'me too/me better in terms of side effect' compound development rather than support the investment and time it requires to translate discoveries at the molecular level into major therapeutic advances (Potter: Personal Communication 2012).

Attention to the high rates of chronic medical illnesses among severely mentally ill patients and the contribution of medication regimens to this phenomenon began to emerge in the 1980s. In 1986, US researchers reported on a study that found that 42% of chronic mentally ill patients had at least one chronic medical problem severe enough to limit functioning (McCarrick, Manderscheid et al. 1986). To confront the large burden of medical comorbidity, the study authors called for psychiatrists 'to become adept at caring for physical illness', and for primary care physicians 'to acquire skill in caring for the mentally ill'. In the US, the separation of mental health from physical health care may have contributed to psychiatrists' lack of attention to the non-neurological consequences of antipsychotic drug exposure, especially in areas that had not traditionally been a focus of concern (eg weight gain, glucose and lipid parameters) (Meyer: Personal Communication 2012).

In 1990, the same year clozapine entered the US and UK markets, US researchers reported on the experience of six of seven clozapine-treated patients who gained 6–69lb (Cohen, Chiles et al. 1990). Authors wrote 'Because of clozapine's anticipated availability in the United States, clinicians should be aware of this possible side effect, which, to the authors' knowledge, has not been reported previously.' Three additional SGAs received FDA approval in the 1990s: risperidone (December, 1993), olanzapine (September, 1996) and quetiapine (September, 1997). All three were rapidly adopted by US psychiatrists, usurping market share from FGAs and establishing themselves as market dominant. While risperidone was the most frequently used of all three for the ensuing decade, the more expensive olanzapine dominated in terms of expenditures (Aparasu and Bhatara 2006). With the surge in SGA utilisation, came a series of studies reporting on glucose and lipid dysregulation among SGA users. The earliest evidence on the glucoregulatory effects of an SGA was published in 1994 as a letter to the editor (Kamran, Doraiswamy et al. 1994).The letter described a case of severe and sustained hyperglycemia in a 41 year old patient with no prior history of diabetes or glucose intolerance who had been treated with clozapine for two months. Other case reports also reporting on clozapine's glucoregulatory effects were published later that year (Kamran, Doraiswamy et al. 1994; Koval, Rames et al. 1994). The earliest evidence on clozapine's lipid effects was published between 1994 and 1996 when a group of researchers reported on increased serum triglyceride levels in clozapine-treated patients (Ghaeli P 1994; Ghaeli P 1995; Ghaeli and Dufresne 1996).

In April 1997, shortly after olanzapine entered the US market (brand name Zyprexa), Gary Tollefson and other Lilly-affiliated researchers published the results of a large *randomised controlled trial* (RCT) (Tollefson, Beasley et al. 1997). In addition to efficacy results, authors reported that olanzapine had a 'substantially more favorable safety profile' than haloperidol. They arrived at this conclusion based on the higher incidence of *extrapyramidal symptoms* (EPS) and prolactin elevation in patients assigned to haloperidol. Notably, they did not comment on the fact that olanzapine was twice more likely to be associated with excessive appetite than haloperidol. In 1997, the *Journal of Clinical*

Psychiatry published a supplement entitled 'Practical issues in using olanzapine' containing the proceedings of a closed symposium, underwritten by an unrestricted educational grant from Eli Lilly, held in Boston in August 1996. While none of the papers in the supplement referred to olanzapine-related glucose or lipid abnormalities, several articles mentioned weight gain as a side effect of the drug. The article on safety of olanzapine reported that across all the active-controlled trials in the company's primary clinical trial database, 41% of the olanzapine subjects had gained 7% or more of body weight (Beasley, Tollefson et al. 1997). However, authors qualified this finding stating that the effect appeared to be largest among those who 'began treatment in an underweight state', the same argument that the company used to successfully lobby the FDA to classify weight gain as an adverse event rather than as the more serious precaution (Food and Drug Administration 30 September, 1996). In his concluding remarks, Tollefson wrote that 'a clear need exists for a novel antipsychotic that will treat a broader spectrum of symptoms beyond typical drugs and do so with less potential for troublesome side effects', by which he referred to EPS, chronic prolactin elevations, agranulocytosis, and arrhythmias (Tollefson 1997).

In August 1997, the FDA issued a 'Guidance for Industry Direct-to-Consumer Rx Drug Promotion' which stated that only advertisements broadcast on television or radio were subjected to the requirement to describe risks and side effects (FDA 1998). From that moment on, print advertisements could omit the side effect summary by directing interested consumers to alternative sources of such information. This decision has been credited for the sharp growth in DTCA for psychiatric drugs (Thomas 1999). In the late 1990s, pharmaceutical companies launched aggressive marketing programmes that promoted antipsychotic drugs among primary care physicians for the treatment of patients of all ages and for uses that in many cases were off-label (Wilson 2010). In February 1998, the New York Times published a piece entitled 'Psychiatric Drugs Are Now Promoted Directly to Patients' which stated that the surge in direct-to-consumer advertising of psychiatric drugs in 1997 had added to the explosive growth of DTCA of prescription drugs (Freudenheim 1998). The article cited a critic who claimed that 'patients who are influenced by the marketing programs may seek out doctors who might be willing to prescribe drugs that are not right for them.' Additionally, the piece referred to a Lilly-sponsored scholarship program for persons with schizophrenia taking zyprexa as 'the most aggressive example of approaching patients directly.' The piece reported that following an inquiry from the paper, Lilly had communicated to the paper that 'upon re-examination', eligibility would no longer be contingent on zyprexa treatment.

A study published in 1998 reporting on several cases of new onset diabetes among patients taking both clozapine and olanzapine provided the earliest evidence of an association between olanzapine and glucose dysregulation (Wirshing, Spellberg et al. 1998). A case report published in 1999 of a bipolar patient who developed new-onset diabetes soon after starting quetiapine provided the earliest evidence on the glucoregulatory effects of quetiapine (Sobel, Jaggers et al. 1999). Also in 1999, the same researchers who had first reported on the association between clozapine and lipid dysregulation reported on the experience of two patients whose serum triglyceride levels increased after being switched from risperidone to clozapine (Ghaeli and Dufresne 1999). A case series published in September 1999 of olanzapine-treated patients who experienced significant increases in weight and triglyceride levels provided the earliest evidence of an association between

olanzapine and lipid dysregulation (Sheitman, Bird et al. 1999). The authors concluded that 'olanzapine treatment may result in a marked increase in triglyceride levels for some patients', recommending monitoring of lipid profiles. A separate group of researchers whose study was published two months later reported similar findings (Osser, Najarian et al. 1999).

The publication in November 1999 of a paper reporting on a comprehensive meta-analysis of the extant evidence on the weight effects of FGAs and SGAs focused attention on the significance of the phenomenon (Allison, Mentore et al. 1999). Partly funded by Pfizer, the study summarized evidence from 81 English- and non-English-language articles reporting on weight changes in antipsychotic-treated patients. The authors found that while placebo was associated with a mean weight reduction of 0.74kg, low-potency FGAs were associated with increases of up to 3.19kg, and SGAs were associated with increases of 4.45kg (clozapine), 4.15kg (olanzapine), 2.92kg (sertindole), 2.10kg (risperidone), and 0.04kg (ziprasidone). Quetiapine's weight effects were not assessed due to lack of sufficient data. The authors discussed the health and adherence implications of their results, suggesting that clinicians consider methods to minimize the impact of antipsychotic-associated weight gain.

Ziprasidone, approved by the US FDA for the treatment of schizophrenia in February, 2001, was one of two SGAs to receive approval in the early 2000s (the other being aripiprazole, approved in November, 2002. Publicly available internal email exchanged by Lilly officials two days after geodon (branded Ziprasidone) received US FDA approval reveals intense concern with geodon's potential for undermining zyprexa's market dominance (Zyprexa-Litigation-Documents 2001). To counter Pfizer's marketing pitch that geodon offered 'SGA efficacy without weight gain', a Lilly official argued that 'nominal response rates (efficacy) and dose-related side-effects and safety concerns (EPS, cardiovascular) make geodon an undesirable first choice as a first agent.' The official added that 'our focus must be to drive home the efficacy of zyprexa –especially at the sales force level. *Safety concerns around EPS and [prolonged] QTc with competitor products need to be elevated while we responsibly manage weight gain objections with data, perspective, and interventions*.' (Italics added).

The expanded use of SGAs for off-label indications in the US was demonstrated by several studies published in the 2000s (eg Rosenheck 2001). This growth meant that large numbers of people were being exposed to the risks of SGAs even when the benefits from exposure were uncertain or unlikely.

In September 2001, the field took a first step toward articulating a response to the growing evidence of metabolic risks of SGAs. That month, at the Mount Sinai Conference, a consensus meeting on the pharmacotherapy of schizophrenia, participants addressed the two-part question of what the focus of clinician monitoring should be when prescribing SGAs, and how the information obtained should influence practice (Marder, Essock et al. 2002). Although no specific monitoring recommendations were issued at that meeting, the question was again taken up at a follow-up meeting.

The breadth of the evidence on the metabolic side effects of SGAs was significantly expanded in the 2000s with the publication of several studies that used a database maintained by the FDA containing adverse events voluntarily reported by clinicians to the

agency's Drug Surveillance System (MedWatch) (Koller, Schneider et al. 2001; Koller, Malozowski et al. 2001; Koller and Doraiswamy 2002; Koller, Cross et al. 2003; Koller, Weber et al. 2004). It is noteworthy that although these studies used data collected by the FDA, they were first-authored by Elizabeth Koller, an endocrinologist then-affiliated with the agency who pursued this research out of her own interest in the area rather than as part of an official FDA psychiatric drug safety review. In fact, the cash-strapped agency dedicates relatively little resources to tracking post-marketing data, and as pointed out by P. M. Doraiswamy, a co-author in the series, while the FDA is under intense pressure to speedily approve new drugs, the agency is not thanked by anyone for detecting new adverse effects (Doraiswamy: Personal Communication 2012). In addition to reporting on new cases or exacerbations of hyperglycemia and diabetes associated with each of the SGAs then available (clozapine, olanzapine, risperidone, quetiapine), the MedWatch studies reported on life-threatening events (ketoacidosis, coma) and deaths plausibly associated with these drugs. In the view of Doraiswamy, these studies made a strong case for causality by showing both the severity of cases and potential reversibility of the reported events when the SGA was removed, as well as the shift in age distribution toward younger ages observed among SGA-treated children and adolescents (Doraiswamy: Personal Communication 2012). The number of fatalities and pattern of serious adverse reports was so striking that it 'shifted the entire debate' on the glucoregulatory effects of SGAs (Doraiswamy: Personal Communication 2012). The first of these studies, published in November 2001, suggested an association between treatment with clozapine and olanzapine and glucose dysregulation (newly diagnosed hyperglycemia and exacerbation of pre-existing diabetes) among children aged 13–18 years (Koller, Malozowski et al. 2001). The authors found that relative to the background rate, the risk for hyperglycemia was tenfold higher for clozapine and comparable for olanzapine, cautioning that 'given that underreporting is typical of these voluntary adverse-event systems, the number of cases may be larger.'

In December 2001, a study reported on fourteen cases of severe hypertriglyceridemia associated with olanzapine and quetiapine therapy, the first to provide evidence on quetiapine's lipid effects (Meyer 2001). The author concluded that 'with the large amassed data demonstrating the link between increased serum triglycerides and cardiovascular risk, one must strongly consider adding periodic assessment of serum lipids during the first year of therapy to the routine monitoring of weight and fasting glucose in patients receiving ongoing treatment with certain [SGAs]'

The third of the MedWatch series of studies, published in July 2002, reported on olanzapine-associated glucoregulatory disturbances (Koller and Doraiswamy 2002). The authors identified 237 cases of newly diagnosed hyperglycemia or diabetes mellitus or exacerbations of pre-existing diabetes, and other serious outcomes including death occurring in close temporal proximity to the hyperglycemic episode, among olanzapine-treated patients. They noted that the number of reported cases, the temporal relationship to the start of olanzapine therapy, the prompt reversibility of hyperglycemia with drug withdrawal in some cases, and the relatively young age and sex ratio of cases suggested that olanzapine may precipitate or unmask diabetes in susceptible patients. In a press related to this publication, co-author Doraiswamy stated 'While our report does not prove a causal relationship between [olanzapine] and diabetes, doctors should be aware of such potentially adverse effects… We have found cases where patients had some very serious problems

associated with olanzapine, and at least 23 of them died' (Health News Digest, 2002; see http://www.women-care.com/viewArticle?ID=370887). The press release received wide coverage around the world, covered not only by major newspapers – including the *Wall Street Journal* as a front page story (WSJ 2003) – but by 'many trade magazines that go to psychiatrists and psychologists' (Doraiswamy: Personal Communication 2012). The press release was important because it was the first time that journalists, advocacy groups, attorneys, nonspecialist physicians, and the general public actually became aware of the scope of the problem (Doraiswamy: Personal Communication 2012). This groundswell of attention pressured both the industry to become more transparent about the metabolic risks of SGAs, and regulators to give priority to this problem. In addition, competitors took notice – as evidenced by the use of these data by the makers of risperidone and ziprasidone to capture Zyprexa's market share – and as a result, routine pharmaceutical promotional activities became yet another venue for clinicians to learn about this liability (Doraiswamy: Personal Communication 2012). A constant through all the MedWatch studies was the rapid onset of serious glucoregulatory abnormalities after the treatment had been instituted, in many instances well before any significant weight gain had occurred. This observation led the authors to state that the mechanism by which these drugs might impair glucose metabolism 'is unlikely to involve weight gain' (Koller, Schneider et al. 2001; Koller and Doraiswamy 2002).

An important step on the road toward generating specific monitoring recommendations for antipsychotic-treated patients was taken in the fall of 2002, when the organisers of the 2001 Mount Sinai Conference convened a follow-up conference with the sole objective of developing 'recommendations for the systematic health monitoring of individuals with schizophrenia for whom antipsychotic medication is prescribed' (Marder, Essock et al. 2002). Unlike the first conference which relied solely on the opinions of schizophrenia experts, the second conference developed a consensus based on discussions with experts in obesity, disease prevention, diabetes, cardiology, endocrinology and ophthalmology. The organisers specifically excluded financial support or participation from the pharmaceutical industry. The conference organisers stated 'the health needs of people with schizophrenia who take antipsychotic medications typically are not adequately addressed by clinicians in specialty mental health programmes or in primary care settings (…), and that a major obstacle to improving the quality of physical health monitoring for patients with schizophrenia is the lack of a consensus regarding which health parameters should be monitored and when they should be monitored.'

Also in 2002, a report on 'Trends in Direct-to-Consumer Advertising of Prescription Drugs' shed some light on the role of DTCA on the growth of SGA use in the US (Frank, Berndt et al. 2002). The authors reported that DTCA spending had grown ninefold between 1994 and 2000 (from $266 million to nearly $2.5 billion) and that based on dollar sales to pharmacies, zyprexa and risperdal (branded risperidone) were among the 20 top selling drugs in 2000. Despite this, they were not among the top 20 drugs for DTCA spending. Although DTCA may not have played a large role in the growth of SGA use in the US until companies began actively marketing SGAs for adjunctive use in major depression from 2008 onwards, pharmaceutical payments to physicians for so-called advisory boards, speaking engagements, and other activities did increase significantly (Meyer: Personal Communication 2012). This phenomenon may have been partly fueled

by the fact that once the SGAs were approved, heavy competition for many years between Janssen, Lilly, AstraZeneca and other companies ensured an enormous supply of money for physician payments as companies reaped billions of dollars in sales (Meyer: Personal Communication 2012).

Responding to the growing evidence on the metabolic side effects of SGAs as well as researchers' calls for monitoring patients' metabolic indices, regulators around the world took action. In 2002, the UK's Committee on Safety of Medicines and the Medicines Control Agency recommended appropriate clinical and blood glucose monitoring in patients with schizophrenia at risk for diabetes (MHRA 2002). Also in 2002, the Pharmaceutical & Food Safety Bureau of the Japanese Ministry of Health, Labor and Welfare ordered a label warning for olanzapine on its risk for serious hyperglycemia, and called for follow-up procedures such as glucose screening during olanzapine treatment (Safety Div/MHLW 2002).

An important milestone in the building of the evidence base on the association between SGAs and metabolic side effects was the publication in 2003 of the first study that used a randomised controlled design to assess the metabolic effects of three SGAs (clozapine, olanzapine, risperidone) and one FGA (haloperidol), among other endpoints (Lindenmayer, Czobor et al. 2003). The authors found that clozapine, olanzapine, and haloperidol were associated with weight-independent increases in mean glucose levels, abnormally high in 14% of cases. In addition, they found that olanzapine and clozapine were associated with increases in mean cholesterol levels. Weight gain was significant and highest for olanzapine, followed by clozapine and risperidone.

In 2003, the growing evidence on the metabolic side effects among SGA-treated patients was amplified by the US news media. In addition to the news pieces on the aforementioned study by Koller and Doraiswamy, the *New York Times* reported in August 2003 that a then unpublished study suggested that patients taking olanzapine, risperidone and quetiapine had a higher risk of developing diabetes than patients taking FGAs (Goode 2003). A revised version of the study was eventually published in 2006 (Lambert, Cunningham et al. 2006).

In September 2003, following in the footsteps of UK and Japanese regulators, the US FDA issued a letter asking manufacturers of all SGAs available in the US market to add text to the WARNINGS section of the product label stating that epidemiological studies 'suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with [SGAs].' The FDA letter added that 'in some cases, the hyperglycemia was extreme and associated with ketoacidosis or hyperosmolar coma or death', also acknowledging that 'the relationship between [SGA] use and hyperglycemia-related adverse events is not completely understood.' Although understandable given the limitations of the evidence at the time, by issuing a class warning rather than a specific warning for olanzapine and clozapine, it is likely that the impact of the label change was somewhat weakened. Nevertheless, the warning made metabolic side effects a high priority for both physicians and patients as well as for researchers, and in effect, diabetes replaced tardive dyskinesia as the new Achilles heel of SGAs (Doraiswamy: Personal Communication 2012). The FDA took much longer to register concerns with other metabolic side effects of SGAs. While for several years following the warning, weight gain and lipid dysregulation

were classified as simple adverse effects in the product labelling, in the late 2000s the agency required that they be listed under the more serious 'precautions' section of the label.

In November 2003, the *American Diabetes Association (*ADA), the *American Psychiatric Association* (APA), the American Association of Clinical Endocrinologists (AACE) and the North American Association for the Study of Obesity (NAASO), convened at a three-day consensus development conference supported in part by grants from AstraZeneca, Bristol-Myers Squibb, Janssen, Lilly, and Pfizer. The focus of the conference was the metabolic side effects of SGAs, and in addition to academic presentations, presentations were delivered by FDA and pharmaceutical company representatives. The conference resulted in a consensus statement that summarised the evidence and contained recommendations for SGA prescribers. This report was considered of such importance that it was simultaneously published in two journals in February 2004: Diabetes Care (American Diabetes Association et al 2004) and the Journal of Clinical Psychiatry (American Diabetes Association et al 2004), marking a rare instance of coordinated duplicated publication (Meyer: Personal Communication 2012). The report stated that the consensus was that the available evidence had multiple limitations, including 'their retrospective nature, heterogeneity of methodology, selection or ascertainment bias, and absence of appropriate or well-characterized control subjects, … relatively short periods of study, … failure to control for a possible treatment sequence bias in 'switchover' studies, and … not always using clinically equivalent dosages of the medications' (American Diabetes Association et al 2004) (American Diabetes Association et al 2004), However, there was also consensus that enough evidence existed to describe the relative metabolic risks of available drugs. 'Clozapine and olanzapine are associated with the greatest weight gain and highest occurrence of diabetes and dyslipidemia. Risperidone and quetiapine appear to have intermediate effects. Aripiprazole and ziprasidone are associated with little or no significant weight gain, diabetes, or dyslipidemia, although they have not been used as extensively as the other agents.' Importantly, the ADA/APA/AACE/NAASO consensus statement recommended baseline screening and monitoring of metabolic parameters in patients prescribed SGAs.

The ADA/APA/AACE/NAASO consensus statement elicited mixed reactions from researchers, clinicians, FDA representatives, and the pharmaceutical industry. In its August 2004 issue, Diabetes Care published a response from two academic researchers who stated that 'the report probably overreaches available evidence when suggesting that clinicians should consider prescribing one antipsychotic over another with the aim of avoiding diabetes. Although clear differences exist in liability for weight gain (and consequently dyslipidemias), quantifiable risk differences among the SGAs regarding an association with diabetes have been inconsistent in large published pharmacoepidemiological studies' (Citrome and Volavka 2004). Another response from two UK-based clinical psychiatrists stated concern 'that some of the matters raised may give an unintentionally misleading message', adding 'we are far from sure, for example, that the evidence supports the view that there is so much disparity in the incidence of obesity and diabetes among FGAs and SGAs' (Isaac and Isaac 2004). That issue also contained a response from representatives of the FDA's Division of Neuropharmacological Drug Products, who wrote that 'Although the (division) agrees with the ADA's recommendation to monitor patients treated with

SGAs for evidence of diabetes, we do not believe that the available evidence allows the ranking of diabetes risk for these drugs at this time' (Boehm, Racoosin et al. 2004). Shortly after the consensus statement was published, in January 2004, Lilly, issued a statement objecting to its conclusions (Lilly 2004). The statement asserted that the company 'does not agree with a controversial conclusion of an opinion paper issued by an ADA-sponsored panel, which states that SGAs differ in their diabetes risk profiles. Not only are these findings not supported by the total body of evidence available on the subject, they are in direct conflict with the FDA's recent class labeling language which states, "Precise risk estimates for hyperglycemia-related adverse events in patients treated with SGAs are not available." The FDA's class labeling decision called on the makers of all SGAs to include a warning on hyperglycemia and diabetes in their prescribing information.'

In addition, in March 2004, the UK's *Medicines and Healthcare products Regulatory Agency* (MHRA) issued a safety warning calling on clinicians to not use risperidone and olanzapine for the management of behavioral problems in older patients with dementia due to high risk of stroke (MHRA 2004). More such warnings aimed at curbing the unsafe off-label use of SGAs would be issued a year later by both MHRA and the FDA.

Although the majority of the evidence pointed to an association between selected SGA use and risk of metabolic disturbance, some studies offered contradictory evidence. A paper published in April 2004 reported on Lilly-funded analyses of data from prospective studies conducted by Lilly-affiliated UK researchers which concluded that there were no differences in the incidence of glucoregulatory abnormalities between placebo cohorts and antipsychotic medication cohorts, or between any of the antipsychotics studied (Bushe and Leonard 2004). The authors concluded that the 'diabetogenic potential ascribed to [SGAs], resulting from retrospective studies, may be incorrect.' It is likely that along with industry-sponsored symposia and other promotional activities directly aimed at physicians, this and other industry-funded studies (eg Bushe and Paton 2005) contributed to obfuscate the emerging evidence on the metabolic effects of SGAs, delaying prescribers and regulators' recognition of the problem (Doraiswamy: Personal Communication 2012). However, intense competition for market share may have also helped to move this research agenda forward. Presumably driven to some extent by their desire to explicitly or implicitly cast their product as a preferable alternative to competing products, pharmaceutical companies have been willing to fund research that NIH and foundations would not fund, and in a nimbler fashion (Allison, Mentore et al. 1999; Henderson, Cagliero et al. 2005; Lambert, Cunningham et al. 2006).

One of the earliest studies on psychiatrists' perceptions regarding the metabolic risks of SGAs and how these perceptions impact therapeutic decision-making was published in October 2004 (Newcomer, Nasrallah et al. 2004). Based on a nationwide survey of 300 randomly selected psychiatrists conducted in 2003, authors found that most respondents recognized weight gain and diabetes mellitus (59% and 51%, respectively) as potential complications of SGA therapy, with many fewer recognizing dyslipidemia and other metabolic events. Notably, 43% of psychiatrists indicated a willingness to risk diabetes for the benefits of SGAs.

In 2004, two major US organisations published guidelines with monitoring recommendations. The APA's second edition of the *Clinical Practice Guideline for the*

Treatment of Patients with Schizophrenia recommended regular measurement of weight/BMI (every visit for six months and at least quarterly thereafter), and indices of glucoregulatory control (fasting glucose or hemoglobin A1c, four months after start of treatment and annually thereafter), rating both recommendations as having substantial clinical confidence (Grade I. The *Guideline* developers also recommended routine monitoring to detect lipid abnormalities (at least every five years) and other obesity-related health problems, rating this recommendation as having moderate clinical confidence (Grade II). For its part, the *Clinical Practice Guideline for Psychosis* developed by the US VA and the Department of Defense recommended assessment of weight, lipids, and glucoregulatory control every 6–12 months during long-term therapy with antipsychotics (Veterans Administration 2004). The *Guideline*'s rationale for this recommendation was that 'antipsychotic medications, in particular (SGAs), may be associated with weight gain and possible dysregulation of blood glucose and lipids.' Guideline developers stated that 'baseline and periodic monitoring of blood glucose, serum lipids, blood pressure and BMI would be prudent particularly in those persons identified as having diabetes, or who are at increased risk for developing diabetes, or those with other known risk factors for cardiovascular disease. These measures may help guide initial selection of antipsychotic medications, improve early detection of the need for medical intervention, and enhance ongoing reevaluation of the appropriateness of psychiatric medications.'

The body of evidence on the metabolic effects of SGAs was strengthened with the publication in January 2005 of a study that assessed measures of glucose dysregulation among non-obese patients with schizophrenia treated with clozapine, olanzapine or risperidone (Henderson, Cagliero et al. 2005). Partially funded by Janssen (maker of risperidone) and conducted by a group of researchers that included diabetes, obesity, and endocrinology experts, the study was important because it sought to determine if the higher incidence of new-onset diabetes in patients with schizophrenia treated with certain SGAs may be the result of a direct effect on glucose metabolism or by their simply increasing known risk factors for diabetes (e.g., via weight gain). They found that in their non-obese study sample, clozapine- and olanzapine-treated subjects had higher rates of glucose dysregulation than risperidone-treated subjects, a finding that supported a direct effect mechanism (ie an effect not mediated by weight gain). They recommended that patients taking clozapine and olanzapine be examined for early precursors of diabetes.

In April 2005, the US FDA asked that all SGA makers add a Boxed Warning and a Bolded Warning section to the product labeling stating that elderly patients with dementia-related psychosis treated with SGAs are at an increased risk of death. In addition, the agency asked all SGA makers except AstraZeneca, the maker of seroquel, to add a warning on the drugs' risks for cerebrovascular adverse events, also stating that the drugs are not approved for the treatment of dementia in elderly patients. Later that year, MHRA, the UK regulator, strengthened its previous safety warning on SGA effects in patients with dementia. The revised warning stated 'The evidence showed that there is a threefold increase in the risk of stroke for risperidone when used in older patients with dementia (and that) there was a similar risk with olanzapine' (MHRA 2005).

The body of evidence on the metabolic effects of SGAs was further boosted with the publication of results from the *Clinical Antipsychotic Trials of Intervention Effectiveness* (CATIE), the largest publicly-funded antipsychotic trial in US history, which had been

planned in 1998 and launched in 1999. Its first major paper was published in September 2005 (Lieberman, Stroup et al. 2005). Although its focus was effectiveness comparisons for olanzapine, quetiapine, risperidone, ziprasidone, and the FGA perphenazine, a key safety finding was that olanzapine was associated with greater weight gain and greater increases in measures of glucose and lipid metabolism than its counterparts. Another important scientific contribution was the publication in 2005 of a comprehensive review of studies that had assessed the metabolic effects of SGAs available in the US and/or Europe (clozapine, olanzapine, risperidone, quetiapine, zotepine, amisulpride, ziprasidone and aripiprazole) (Newcomer 2005). Regarding weight gain, the author concluded that based on RCT evidence, clozapine and olanzapine are associated with the greatest risk of clinically significant weight gain, with other agents producing relatively lower levels of risk. The author's review of uncontrolled observations, large retrospective database analyses, and RCTs and other controlled experimental studies led him to conclude that SGAs are also associated with differing effects on glucose and lipid metabolism. He wrote that there was 'generally consistent evidence that clozapine and olanzapine treatment are associated with an increased risk of diabetes mellitus and dyslipidaemia. Inconsistent results, and a generally smaller effect in studies where an effect is reported, suggest limited if any increased risk for treatment-induced diabetes mellitus and dyslipidaemia during risperidone treatment, despite a comparable volume of published data. A similarly smaller and inconsistent signal suggests limited if any increased risk of diabetes or dyslipidaemia during quetiapine treatment, but this is based on less published data than is available for risperidone.' Largely based on clinical trial data, the author found no evidence suggesting that ziprasidone and aripiprazole treatment are associated with an increase in metabolic risk.

The earliest of a series of legal developments that, unlike other developments unrelated to litigation, may have played an important role in modifying clinical practice, burst on the public scene in June 2005. That month, at the conclusion of the first US lawsuit filed against the pharmaceutical industry in connection with SGA marketing practices, Lilly agreed to pay $690 million to settle liability claims filed by 8,000 plaintiffs based on allegations that zyprexa caused side effects related to diabetes and hyperglycemia (Pritchard 2005). This settlement was followed by an agreement in December 2006 by Bristol-Myers Squibb to pay $499 million to settle civil lawsuits for alleged fraudulent marketing of abilify (branded aripiprazole) for off-label uses, including use in children and to treat dementia-related psychosis (Schmit 2006).

A paper reporting on the final findings of a study partly funded by Bristol-Myers Squibb – the maker of aripiprazole – that was the subject of the August 2003 New York Times piece mentioned above was published in October 2006 (Lambert, Cunningham et al. 2006). The authors used a large national sample of US VA patients with schizophrenia and no preexisting diabetes to assess risk of new-onset Type 2 diabetes associated with long-term use of olanzapine, risperidone, quetiapine, or the FGA haloperidol during the period 1999–2001. They found that relative to patients initiating haloperidol, diabetes risk was increased equally with new use of olanzapine, risperidone, or quetiapine, concluding that 'assuming that the observed associations are causal, approximately one third of new cases of diabetes may be attributed to use of olanzapine, risperidone, and quetiapine in patients taking these medications.'

A CATIE study reporting on rates of treatment for diabetes, dyslipidemia, and hypertension for study subjects at the time of enrollment and published in September 2006, called attention to 'the high likelihood that metabolic disorders are untreated in patients with schizophrenia', particularly for hypertension and dyslipidemia (Nasrallah, Meyer et al. 2006).

The growing evidence of higher metabolic risk for people with schizophrenia treated with certain SGAs, regulators' warnings, and monitoring recommendations, spawned research on attitudes toward and actual adherence to these recommendations. A study published in December 2006 reported on a survey of US psychiatrists' attitudes and practices regarding metabolic monitoring (Ketter and Haupt 2006). Conducted in the winter of 2005–2006 and rather limited by a low response rate and self-selection of respondents, the authors found that more than 80% of respondents reported monitoring weight, fasting plasma glucose level, and fasting lipid profile at regular intervals after initiating new medications for bipolar disorder, SGAs among them. Further, respondents viewed clozapine and olanzapine as highly problematic, and quetiapine and risperidone as minimally to moderately problematic in terms of weight gain and metabolic issues. These encouraging findings stood in contrast with the findings of a UK study published in May 2007 that assessed annual rates of metabolic monitoring among SGA users through a review of medical records conducted in 2006 (Barnes, Paton et al. 2007). The authors found low documented assessment rates of 26% for blood pressure, 17% for weight, 28% for glucose or hemoglobin A1c, 22% for lipids, and 11% for all 4 measures.

Further legal developments occurred in 2007. In January that year, Lilly settled several lawsuits. As reported by the New York Times, 'Eli Lilly agreed yesterday to pay up to $500 million to settle 18,000 lawsuits from people who claimed they had developed diabetes or other diseases after taking zyprexa. Including earlier settlements over zyprexa, Lilly has now agreed to pay at least $1.2 billion to 28,500 people who said they were harmed by the drug. At least 1,200 suits are still pending, the company said. About 20 million people worldwide have taken zyprexa since its introduction in 1996' (Berenson 2007). In June 2007, Lilly settled 900 additional class action lawsuits in connection with zyprexa product liability. In 2008, an investigation of Lilly filed by 33 states in the US ended in an injunction calling Lilly to pay $52 million as well as conform to restrictions and reforms regarding marketing and promotion of zyprexa. By 2008, after pleading guilty to criminal charges of unlawful promotion of zyprexa, Lilly had paid $515 million in fines, in addition to $800 million for the settlement of a federal civil investigation (Goldstein 2009).

An important research synthesis of the effectiveness of SGAs for off-label indications was published by the US Agency for Healthcare Research and Quality in January 2007 (Shekelle P 2007). The authors reported that the most common off-label uses of SGAs were treatment of agitation in dementia and treatment of depression, obsessive-compulsive disorder, posttraumatic stress disorder, personality disorders, Tourette's syndrome and autism, and found 'very little strong evidence' that SGAs are effective in the treatment of those disorders. A recently published update of this review found that aripiprazole, olanzapine and risperidone provided small but statistically significant benefits for symptoms associated with dementia (psychosis, mood alterations, and aggression) (Maglione 2011). Additionally, quetiapine was associated with benefits for symptoms of

generalized anxiety disorder, and risperidone for obsessive-compulsive disorder symptoms. However, the authors noted that adverse events were common.

The possible contribution of legal developments to the recognition of the adverse effects of SGAs and other drugs was discussed in a paper published in JAMA in January 2007 entitled 'The role of litigation in defining drug risks' (Kesselheim and Avorn 2007). The authors stated that litigation brought by government agencies and patients 'can help uncover previously unavailable data on adverse effects, questionable practices by manufacturers, and flaws in drug regulatory systems.' Regarding zyprexa – which they profiled along with seven other drugs – they wrote that 'Lilly initially understated (zyprexa-related) weight gain and diabetes', and that litigation played an important role in regulators' decision to revise drug labeling and mandate changes in drug promotional strategies 'to clarify risk'. The authors also referred to evidence revealing that 'Lilly long downplayed and kept secret research that linked use of the drug to weight gain and hyperglycemia.'

A study entitled 'Who are the new users of antipsychotic medications?' published in May 2008 illustrated the dramatic growth of SGA use in the US since the introduction of olanzapine (Domino and Swartz 2008). The authors found that between 1996–97 and 2004–05, the prevalence of SGA use increased almost sevenfold to 1.06%, whereas FGA use dropped fourfold to 0.15% in the non-institutionalised US population. Further, they found that the rapid diffusion of SGAs did not occur among persons with schizophrenia but, rather, it occurred for off-label uses and newer on-label conditions, particularly among children.

CATIE researchers added to the scientific evidence on the metabolic effects of SGAs with a paper published in April 2008 which reported on three month changes in metabolic parameters among trial participants whose metabolic syndrome (MS) status could be re-assessed (Meyer, Davis et al. 2008). The authors found that MS prevalence increased for olanzapine (from 34.8% to 43.9%) but decreased for ziprasidone (from 37.7% to 29.9%). Further, they found that while olanzapine and quetiapine had the largest mean increases in waist circumference, followed by risperidone, waist circumference was unchanged for ziprasidone and it decreased for perphenazine. Olanzapine also demonstrated significantly different changes in fasting triglycerides (+21.5 mg/dl) compared to ziprasidone (–32.1 mg/dl). Despite the significance of the evidence generated by the CATIE trial, a paper published in July 2008 showed that it had reached only a fraction of its target audience. The paper reported on a survey of US psychiatrists conducted in the fall of 2006 whose main finding was that only one in two psychiatrists with expertise in schizophrenia were familiar with the main findings of the trial (Petersen, Huffman et al. 2008).

Concern in the US over the impact of SGA treatment on the overall health status of people with severe mental illnesses led the *National Association of State Mental Health Program Directors* (NASMHPD), an organisation representing the leadership of states' public mental health service systems, to join in the call for increasing the rate of metabolic monitoring in antipsychotic-treated patients. NASMPHD sponsored a technical report published in October 2008 whose main focus was the measurement of health status in this population (Mauer 2008). The report alluded to the ADA/APA/AACE/NAASO consensus statement and stated that 'despite having been available for four years, these ADA/APA

guidelines are generally not followed.' This contention was supported with results from several studies, including a study that found that among California Medicaid beneficiaries with a newly prescribed SGA, only 28% and 43% had glucose and lipid testing, respectively, in the six months following the start of the medication. The paper was eventually published in January 2010 (Barnett, VonMuenster et al. 2010). Additional US studies provided further evidence on the significance of the problem. One of them, published in June 2009 and entitled 'Metabolic screening after the American Diabetes Association's Consensus Statement on antipsychotic drugs and diabetes', reported low annual rates of glucose and lipid testing (38% and 23%, respectively) among SGA users enrolled in a US commercial health plan during the period January 2001 – December 2006 (Morrato, Newcomer et al. 2009). The authors concluded that although 'a gradual increase in screening rates occurred over the six year period, the changes were not temporally associated with the ADA statement.'

A paper published in October 2009 reporting on a study of metabolic effects of SGAs in children and adolescents received wide media attention because of the study's alarming weight gain findings in a population for whom SGA use is largely off-label (Rockoff 2009; Wilson 2009). Conducted between December 2001 and September 2007, the study assessed short-term metabolic changes in SGA users aged 4–19 years, of whom only 30% were diagnosed with schizophrenia (Correll, Manu et al. 2009). The authors found that in the course of the twelve week trial, significant weight gain of ≥7% occurred in 84% of patients on olanzapine, 64% on risperidone, 58% on aripiprazole, 56% on quetiapine, and 0% of control subjects. With olanzapine, all glucose and lipid indices increased significantly, only lipid indices increased significantly with quetiapine, and only triglycerides increased significantly with risperidone. Metabolic changes were non-significant with aripiprazole and comparison subjects.

The policy challenges associated with the broadened use of SGAs in the US was the focus of a paper published in the fall of 2009 in a prestigious US policy journal (Crystal 2009). The authors stated that SGAs are now used 'for a wide range of clinical indications in diverse populations, including privately and publicly insured youth and elderly nursing home residents', and that among nonelderly adults, their use has broadened 'beyond the traditional core treated population of people with schizophrenia.' The authors added that 'although off-label use is common for many classes of drugs and does not necessarily by itself imply a quality concern, it is particularly prevalent in the antipsychotic class.'

Important new legal developments involving SGA makers occurred in 2009 and 2010. In September 2009, the US Department of Justice ordered Pfizer to pay $2.3 billion in criminal and civil fines for illegal promotion of geodon and other products, and in addition, the company was placed under monitoring for five years by the US Department of Health and Human Services (Barrett 2009). In April 2010, Astrazeneca agreed to pay $520 million to settle a probe by the US Attorney's Office in Philadelphia over allegations of illegal off-label promotion of seroquel (branded quetiapine). In August 2010, Astrazeneca paid an additional $198 million to settle 17,500 cases brought by patients claiming side effects from seroquel.

Further evidence on the problematic low rates of metabolic monitoring among US SGA users was provided by a paper published in January 2010 entitled 'Metabolic testing rates

in 3 state Medicaid programs after FDA Warnings and ADA/APA recommendations for second-generation antipsychotic drugs' (Morrato, Druss et al. 2010). The authors found that initial testing rates for SGA-treated patients were low (glucose, 27%; lipids, 10%), and that the FDA warning had no impact on glucose testing and only a small impact on lipid testing as evidenced by a marginal increase in rates. However, the authors found that new olanzapine prescriptions declined significantly during the study period. The authors concluded that although baseline glucose and lipid testing for SGA-treated patients was infrequent and showed little change following the diabetes warning and monitoring recommendations, there was a change in SGA drug selection consistent with intentions to reduce metabolic risk. They further posited that 'the main effect of the FDA warning was to accelerate a decline in olanzapine prescribing, consistent with intentions to reduce metabolic risk, rather than to increase metabolic laboratory monitoring.' In their discussion of possible explanations for the low testing rates, the authors mentioned lack of awareness among psychiatrists, but pointed out that surveys conducted after the warning suggested high levels of knowledge of the metabolic risks associated with SGA and the need for metabolic monitoring (Buckley, Miller et al. 2005; Ketter and Haupt 2006; Suppes, McElroy et al. 2007). They also mentioned lack of resources for ordering blood tests in certain publicly-funded settings, but cited evidence that most community mental health centres surveyed for a study on medical services for mentally ill people in the US reported having protocols or procedures to screen for common medical problems such as diabetes (Druss, Marcus et al. 2008), and that testing rates have been found to be similar in commercially insured (eg Morrato, Newcomer et al. 2009) and VA populations (Hsu, Ried et al. 2008). Lastly, they hypothesised that psychiatrists – the primary target audience for risk communication – may be aware of the warnings, but that less awareness may exist among primary care providers, the clinicians most likely to order tests and provide general medical care to SGA users in the US. Citing a study that showed that patients who were prescribed SGAs by a psychiatrist were less likely to receive testing than if the drug was prescribed by a primary care provider (Haupt, Rosenblatt et al. 2009), the authors wrote that 'diffusion theory predicts that it is difficult to make a change that is partly dependent on someone else to execute' (Morrato, Druss et al. 2010). The overarching systems issue in this regard is the fact that in the US, most people with severe mental illnesses are cared for in the specialty care sector, and as a result of multiple barriers, clinical coordination between specialists and primary care providers is poor (Horvitz-Lennon, Kilbourne et al. 2006).

Inadequacies in the management of adverse effects of SGAs in the US were further highlighted by a paper published in July 2010 reporting on a study conducted in 2002 and 2003 at three large VA clinics in California (Young, Niv et al. 2008). The authors found that 46% of antipsychotic-treated patients had elevated weight; that weight management improved over time but only modestly; and that odds of improved management were higher when psychiatrists had more patients with schizophrenia in their caseloads. In addition, compared to results from a study they had conducted in the 1990s (when FGAs were more frequently used), the authors found that treatment rarely changed in response to weight gain in both studies yet the need for treatment changes was greater in the more current study due to the higher frequency of treatment-emergent weight gain. They concluded that 'there is a need for interventions that improve management of psychosis and weight.'

NICE, an influential developer of clinical guidelines in the UK, published an *Updated Clinical Guideline on Schizophrenia* in 2010 which provided recommendations regarding metabolic monitoring (NICE 2010). The guideline recommended that general practitioners and other first-line healthcare professionals monitor the physical health of people with schizophrenia at least once a year, also recommending that those 'at increased risk of developing cardiovascular disease and/or diabetes be identified at the earliest opportunity.' Although the guideline did not specify the type/grade of evidence for each recommendation, it stated that the 'guidance is based on the best available evidence.'

An improved situation regarding rates of metabolic monitoring in the US was profiled by a study published in June 2010 that evaluated the quality of VA mental health services during fiscal year 2007 and found that 85% and 78% of veterans had had glucose and lipid testing, respectively (Watkins, Keyser et al. 2010). Rates were nearly identical for veterans receiving antipsychotic medication. Two UK papers published in 2011 provided mixed evidence on important components of a well-functioning system of care for people with severe mental illnesses. One of them evaluated the content and quality of screening guidelines for cardiovascular risk in schizophrenia and found that four of eighteen guidelines were of good quality (De Hert, Vancampfort et al. 2011). Additionally, a study conducted by Irish investigators showed that a vast majority of general practitioners (ie primary care providers) were willing to manage the metabolic dysregulations associated with antipsychotics prescribed by specialists (Bainbridge, Gallagher et al. 2011). However, a paper published in 2012 reported that a meta-analysis of 48 studies conducted between 2000 and 2011 in the UK, US, Canada, Spain, and Australia had found concerning low rates of metabolic monitoring in patients prescribed antipsychotic drugs (Mitchell, Delaffon et al. 2012).

The growth in SGA use in the US was further documented in 2011 with the publication of findings from analyses of office-based visits for the period 1995–2008 which indicated that 'a pronounced shift in the use' of SGAs had occurred during that thirteen year period (Alexander, Gallagher et al. 2011). The authors found a 45% decrease in the proportion of use for schizophrenia, and a nearly sevenfold increase in use for bipolar disorder, representing a third of all SGA uses in 2008.

6.7 Observations

Some of the factors that may have acted as **barriers** to the prompter recognition of the metabolic side effects of SGAs or a prompter response from organised psychiatry and antipsychotic prescribers include:

- Pharmaceutical industry *obstructionism*, as evidenced by systematic understating and withholding of safety evidence by some SGA makers, and *obfuscation*, as evidenced by substantial financial support for symposia and research suggesting that safety concerns were exaggerated as well as payments to key opinion leaders for their participation in SGA-related consulting and speaking opportunities (Meyer: Personal Communication 2012).
- In the US, the absence of incentives for physicians to report adverse events leading to underreporting of such events (Doraiswamy: Personal Communication 2012).

- In the US, the FDA's relative lack of resources for tracking or investigating post-marketing data, and contrast between the absence of incentives for the agency to focus on adverse effects and its vulnerability to industry's lobbying efforts aimed at thwarting regulatory action (Doraiswamy: Personal Communication 2012).

- In the US and in connection with the 2003 warning issued by the FDA, the agency's decision to issue a *class* warning (as opposed to a drug-specific warning), and its *decision* to not issue a higher-level (*black box*) warning.

- The political and socioeconomic disenfranchisement and stigma in the patient population that has borne the brunt of SGA metabolic side effects (Doraiswamy: Personal Communication 2012).

- Psychiatry's intense focus on the neurological side effects of higher potency FGAs at the time when the most metabolically active SGAs entered the market, may have positively predisposed the field toward the latter drugs given that most of them had notably lower rates of such side effects (Meyer: Personal Communication 2012).

- Regulators' and clinicians' concerns with hyperprolactinemia (risperidone, olanzapine, quetiapine); cataracts (quetiapine); and QTc prolongation (ziprasidone) distracted the field from the metabolic effects of SGAs (Nasrallah: Personal Communication 2012).

- In the US, the separation of mental health care from physical health care may have contributed to poor coordination between psychiatrists and primary care providers around the physical health care needs of people with schizophrenia (Horvitz-Lennon, Kilbourne et al. 2006), and to psychiatrists' lack of attention to the non-neurological consequences of antipsychotic drug exposure (Meyer: Personal Communication 2012).

Some of the factors that may have **facilitated** the recognition of SGA metabolic side effects or an adequate response to deal with those side effects include:

- Litigation and malpractice concerns, which not only affected marketing practices but may have also played a leading role in the observed changes in clinical practice (prescribing patterns, and monitoring of metabolic parameters) (Allison: Personal Communication 2012) (Meyer: Personal Communication 2012).

- Pharmaceutical companies' willingness to fund research that NIH and foundations would not fund, and in a nimbler fashion (Allison: Personal Communication 2012).

- The contribution of researcher-clinicians whose patients developed metabolic side effects associated with SGA treatment.

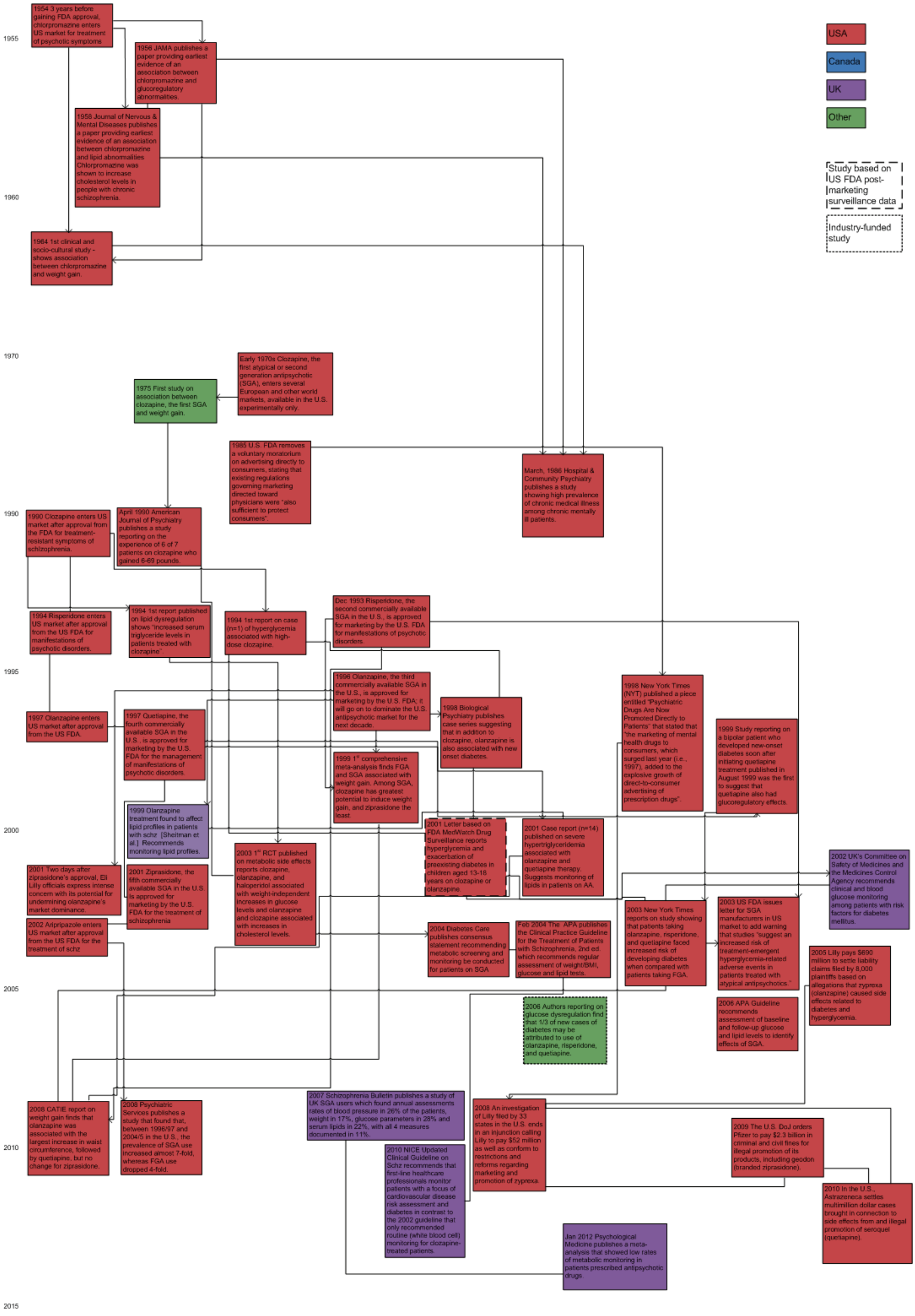
- Multi-disciplinary research collaborations between psychiatrists, obesity specialists, endocrinologists.

6.8 Other observations of relevance to this case study

- Although hard to demonstrate empirically, it does not appear that the recognition of the metabolic side effects associated with SGAs or the response to those side effects

was slower than the recognition and response to side effects of other drugs, whether psychiatric or not (Doraiswamy: Personal Communication 2012).

- The FDA's standards for market approval – namely, the relative ease of meeting non-inferiority criteria – subtly work against the field investing in better ways to demonstrate superiority of one compound over another in the complex realm of clinical efficacy. Additionally, current patent law in the US offers little incentive for companies to pursue evidence of superiority, instead favoring 'me too/me better in terms of side effect' compound development (Potter: Personal Communication 2012)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1954 3 years before gaining FDA approval, chlorpromazine enters US market for treatment of psychotic symptoms
1956 JAMA publishes a paper providing earliest evidence of an association between chlorpromazine and glucoregulatory abnormalities.
1958 Journal of Nervous & Mental Diseases publishes a paper providing earliest evidence of an association between chlorpromazine and lipid abnormalities. Chlorpromazine was shown to increase cholesterol levels in people with chronic schizophrenia.
1964 1st clinical and socio-cultural study - shows association between chlorpromazine and weight gain.
Early 1970s Clozapine, the first atypical or second generation antipsychotic (SGA), enters several European and other world markets, available in the U.S. experimentally only.
1975 First study on association between clozapine, the first SGA and weight gain.
1985 U.S. FDA removes a voluntary moratorium on advertising directly to consumers, stating that existing regulations governing marketing directed toward physicians were "also sufficient to protect consumers".
March, 1986 Hospital & Community Psychiatry publishes a study showing high prevalence of chronic medical illness among chronic mentally ill patients.
1990 Clozapine enters US market after approval from the FDA for treatment-resistant symptoms of schizophrenia.
April 1990 American Journal of Psychiatry publishes a study reporting on the experience of 6 of 7 patients on clozapine who gained 6-69 pounds.
1994 Risperidone enters US market after approval from the US FDA for manifestations of psychotic disorders.
1994 1st report published on lipid dysregulation shows "increased serum triglyceride levels in patients treated with clozapine".
1994 1st report on case (n=1) of hyperglycemia associated with high-dose clozapine.
Dec 1993 Risperidone, the second commercially available SGA in the U.S., is approved for marketing by the U.S. FDA for manifestations of psychotic disorders.
1996 Olanzapine, the third commercially available SGA in the U.S., is approved for marketing by the U.S. FDA; it will go on to dominate the U.S. antipsychotic market for the next decade.
1997 Olanzapine enters US market after approval from the US FDA.
1997 Quetiapine, the fourth commercially available SGA in the U.S., is approved for marketing by the U.S. FDA for the management of manifestations of psychotic disorders.
1998 Biological Psychiatry publishes case series suggesting that in addition to clozapine, olanzapine is also associated with new onset diabetes.
1998 New York Times (NYT) published a piece entitled "Psychiatric Drugs Are Now Promoted Directly to Patients" that stated that "the marketing of mental health drugs to consumers, which surged last year (i.e., 1997), added to the explosive growth of direct-to-consumer advertising of prescription drugs".
1999 1st comprehensive meta-analysis finds FGA and SGA associated with weight gain. Among SGA, clozapine has greatest potential to induce weight gain, and ziprasidone the least.
1999 Study reporting on a bipolar patient who developed new-onset diabetes soon after initiating quetiapine treatment published in August 1999 was the first to suggest that quetiapine also had glucoregulatory effects.
1999 Olanzapine treatment found to affect lipid profiles in patients with schz [Sheitman et al.] Recommends monitoring lipid profiles.
2001 Letter based on FDA MedWatch Drug Surveillance reports hyperglycemia and exacerbation of preexisting diabetes in children aged 13-18 years on clozapine or olanzapine.
2001 Case report (n=14) published on severe hypertriglyceridemia associated with olanzapine and quetiapine therapy. Suggests monitoring of lipids in patients on AA.
2001 Two days after ziprasidone's approval, Eli Lilly officials express intense concern with its potential for undermining olanzapine's market dominance.
2001 Ziprasidone, the fifth commercially available SGA in the U.S. is approved for marketing by the U.S. FDA for the treatment of schizophrenia
2002 Aripiprazole enters US market after approval from the US FDA for the treatment of schz
2003 1st RCT published on metabolic side effects reports clozapine, olanzapine, and haloperidol associated with weight-independent increases in glucose levels and olanzapine and clozapine associated with increases in cholesterol levels.
2002 UK's Committee on Safety of Medicines and the Medicines Control Agency recommends clinical and blood glucose monitoring among patients with risk factors for diabetes mellitus.
2003 New York Times reports on study showing that patients taking olanzapine, risperidone, and quetiapine faced increased risk of developing diabetes when compared with patients taking FGA.
2003 US FDA issues letter for SGA manufacturers in US market to add warning that studies "suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics."
2004 Diabetes Care publishes consensus statement recommending metabolic screening and monitoring be conducted for patients on SGA
Feb 2004 The APA publishes the Clinical Practice Guideline for the Treatment of Patients with Schizophrenia, 2nd ed. which recommends regular assessment of weight/BMI, glucose and lipid tests.
2005 Lilly pays $690 million to settle liability claims filed by 8,000 plaintiffs based on allegations that zyprexa (olanzapine) caused side effects related to diabetes and hyperglycemia.
2006 Authors reporting on glucose dysregulation find that 1/3 of new cases of diabetes may be attributed to use of olanzapine, risperidone, and quetiapine.
2006 APA Guideline recommends assessment of baseline and follow-up glucose and lipid levels to identify effects of SGA.
2007 Schizophrenia Bulletin publishes a study of UK SGA users which found annual assessments rates of blood pressure in 26% of the patients, weight in 17%, glucose parameters in 28% and serum lipids in 22%, with all 4 measures documented in 11%.
2008 CATIE report on weight gain finds that olanzapine was associated with the largest increase in waist circumference, followed by quetiapine, but no change for ziprasidone.
2008 Psychiatric Services publishes a study that found that, between 1996/97 and 2004/5 in the U.S., the prevalence of SGA use increased almost 7-fold, whereas FGA use dropped 4-fold.
2008 An investigation of Lilly filed by 33 states in the U.S. ends in an injunction calling Lilly to pay $52 million as well as conform to restrictions and reforms regarding marketing and promotion of zyprexa.
2009 The U.S. DoJ orders Pfizer to pay $2.3 billion in criminal and civil fines for illegal promotion of its products, including geodon (branded ziprasidone).
2010 In the U.S., Astrazeneca settles multimillion dollar cases brought in connection to side effects from and illegal promotion of seroquel (quetiapine).
2010 NICE Updated Clinical Guideline on Schz recommends that first-line healthcare professionals monitor patients with a focus of cardiovascular disease risk assessment and diabetes in contrast to the 2002 guideline that only recommended routine (white blood cell) monitoring for clozapine-treated patients.
Jan 2012 Psychological Medicine publishes a meta-analysis that showed low rates of metabolic monitoring in patients prescribed antipsychotic drugs.
USA
Canada
UK
Other
Study based on US FDA post-marketing surveillance data
Industry-funded study

6.9 References

Alexander, G. C., Gallagher, S. A. , et al. (2011). 'Increasing off-label use of antipsychotic medications in the United States.' *Pharmacoepidemiology and Drug Safety* 20(2), 177–184.

Allison, D. B., Mentore, J. L., et al. (1999). 'Antipsychotic-induced weight gain: a comprehensive research synthesis.' *The American Journal of Psychiatry* 156(11), 1686–1696.

Allison: Personal Communication (2012).

American Diabetes Association, et al. (2004). 'Consensus development conference on antipsychotic drugs and obesity and diabetes.' *Journal of Clinical Psychiatry* 65(2), 267–272.

American Diabetes Association, et al. (2004). 'Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes.' *Diabetes Care* 27(2), 596–601.

Aparasu, R. R. and V. Bhatara (2006). 'Antipsychotic use and expenditure in the United States.' *Psychiatric Services* 57(12), 1693.

Arranz, B., P. Rosel, et al. (2004). 'Insulin resistance and increased leptin concentrations in noncompliant schizophrenia patients but not in antipsychotic-naive first-episode schizophrenia patients.' *The Journal of Clinical Psychiatry* 65(10), 1335–1342.

Ayd, F. J. (1961). 'A survey of drug-induced extrapyramidal reactions.' *The Journal of the American Medical Association* 175(12), 1054–1060.

Bainbridge, E., Gallagher, A., et al. (2011). 'General practitioners' attitudes on who should manage metabolic dysregulations associated with antipsychotics.' *The Psychiatrist* 35(6), 213–215.

Ban, T. A. (2007). 'Fifty years of chlorpromazine: A historical perspective.' *Neuropsychiatric Disease and Treatment* 3(4), 495–500.

Barnes, T. R., Paton, C., et al. (2007). 'A UK audit of screening for the metabolic side effects of antipsychotics in community patients.' *Schizophrenia Bulletin* 33(6), 1397–1403.

Barnett, M., VonMuenster, S., et al. (2010). 'Assessment of monitoring for glucose and lipid dysregulation in adult Medi-Cal patients newly started on antipsychotics.' *Annals of Clinical Psychiatry* 22(1), 9–18.

Barrett, D. (2009). 'Pfizer to pay record $2.3B penalty over promotions.' *Associated Press*.

Beasley, C. M., Jr., Tollefson, G. D., et al. (1997). 'Safety of olanzapine.' *Journal of Clinical Psychiatry* 58 (Suppl. 10), 13–17.

Berenson, A. (2007). 'Lilly to Pay Up to $500 Million to Settle Claims.' *New York Times*.

Boehm, G., Racoosin, J. A., et al. (2004). 'Consensus development conference on antipsychotic drugs and obesity and diabetes: response to consensus statement.' *Diabetes Care* 27(8), 2088–2089; author reply 2089–2090.

Buckley, P. F., Miller, D. D., et al. (2005). 'Clinicians' recognition of the metabolic adverse effects of antipsychotic medications.' *Schizophrenia Research* 79(2-3), 281–288.

Bushe, C. and Leonard, B. (2004). 'Association between atypical antipsychotic agents and Type 2 diabetes: review of prospective clinical data.' *British Journal of Psychiatry Supplement* 47, S87–93.

Bushe, C. and Paton, C. (2005). 'The potential impact of antipsychotics on lipids in schizophrenia: is there enough evidence to confirm a link?' *Journal of Psychopharmacology* 19(6 Suppl.), 76–83.

Citrome, L. and Volavka, J. (2004). 'Consensus development conference on antipsychotic drugs and obesity and diabetes: response to consensus statement.' *Diabetes Care* 27(8), 2087–2088; author reply 2089–2090.

Clark ML, J. P. (1960). 'Amenorrhea and elevated serum cholesterol produced by a trifluoro-methylated phenothiazine.' *Journal of Clinical Endocrinology and Metabolism* 20, 641–646.

Cohen, S., Chiles, J., et al. (1990). 'Weight gain associated with clozapine.' *The American Journal of Psychiatry* 147(4), 503–504.

Correll, C. U., Manu, P. et al. (2009). 'Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents.' *The Journal of the American Medical Association* 302(16), 1765–1773.

Crystal, S. O., Huang, C., Pincus, H. and Gerhard, T., (2009). 'Broadened Use Of Atypical Antipsychotics: Safety, Effectiveness, And Policy Challenges.' *Health Affairs (Millwood)* 28(5), 770–781.

De Hert, M., Vancampfort, D., et al. (2011). 'Guidelines for screening and monitoring of cardiometabolic risk in schizophrenia: systematic evaluation.' *British Journal of Psychiatry* 199(2), 99–105.

Domino, M. E. and Swartz, M. S., (2008). 'Who are the new users of antipsychotic medications?' *Psychiatric Services* 59(5), 507–514.

Doraiswamy: Personal Communication (2012).

Druss, B. G., Marcus, S. C., et al. (2008). 'Medical services for clients in community mental health centers: results from a national survey.' *Psychiatric Services* 59(8), 917–920.

Faurbye, A. and Clausen, J. (1964). 'Changes in serum proteins and cerebrospinal fluid proteins during pharmacotherapy of psychoses.' *Acta Psychiatrica Scandinavica* 40(1), 107–116.

FDA, U. (1995). Fed. Reg. 42581, 42582. F. notice.

FDA, U. (1998). 21 U.S.C. §§ 352(a).

FDA, U. (2010). Guidance for Industry Non-Inferiority Clinical Trials.

Fleischhacker, W. W., Stuppack, C., et al. (1986). 'Fluperlapine vs haloperidol: a comparison of their neuroendocrinological profiles and the influence on serum lipids.' *Pharmacopsychiatry* 19(3), 111–114.

Food and Drug Administration (30 September 1996). *Approval Recommendation on NDA 20–592: Zyprexa [Olanzapine]*. Washington, DC.

Frank, R., Berndt, E., et al. (2002). *Trends in Direct-to-Consumer Advertising of Prescription Drugs*, Kaiser Family Foundation.

Freudenheim, M. (1998). Psychiatric Drugs Are Now Promoted Directly to Patients. *New York Times*.

GAO, U. (2010) 'New Drug Approval FDA's Consideration of Evidence from Certain Clinical Trials.'

Ghaeli P. D. R. (1994). 'Increased serum triglyceride levels in patients treated with clozapine.' *International Pharmaceutical Abstracts* 31, 2243.

Ghaeli P. D. R. (1995). 'Elevated serum triglycerides on clozapine resolve with risperidone.' *Pharmacotherapy* 15, 382–385.

Ghaeli, P. and Dufresne, R. L. (1996). 'Serum triglyceride levels in patients treated with clozapine.' *American Journal of Health-System Pharmacy* 53(17), 2079–2081.

Ghaeli, P. and Dufresne, R. L. (1999). 'Elevated serum triglycerides with clozapine resolved with risperidone in four patients.' *Pharmacotherapy* 19(9), 1099–1101.

Goldstein, S. (2009). 'Eli Lilly to pay $1.4 billion to settle Zyprexa suits.' *MarketWatch*.

Goode, E. (2003). '3 Schizophrenia Drugs May Raise Diabetes Risk, Study Says.' *New York Times*.

Haupt, D. W. and Newcomer, J. W. (2001). 'Hyperglycemia and antipsychotic medications.' *Journal of Clinical Psychiatry* 62 Suppl 27, 15–26; discussion 40–11.

Haupt, D. W., Rosenblatt, L. C., et al. (2009). 'Prevalence and predictors of lipid and glucose monitoring in commercially insured patients treated with second-generation antipsychotic agents.' *The American Journal of Psychiatry* 166(3), 345–353.

Hemphill, R. E., Pascoe, F. D., et al. (1975). 'An investigation of clozapine in the treatment of acute and chronic schizophrenia and gross behaviour disorders.' *South African Medical Journal* 49(51), 2121–2125.

Henderson, D. C., Cagliero, E., et al. (2005). 'Glucose metabolism in patients with schizophrenia treated with atypical antipsychotic agents: a frequently sampled intravenous glucose tolerance test and minimal model analysis.' *Archives of General Psychiatry* 62(1), 19–28.

Hiles, B. (1956). 'Hyperglycemia and glycosuria following chlorpromazine therapy.' *The Journal of the American Medical Association* 162, 1651.

Horvitz-Lennon, M., Kilbourne, A. M., et al. (2006). 'From silos to bridges: meeting the general health care needs of adults with severe mental illnesses.' *Health Affairs (Millwood)* 25(3), 659–669.

Hsu, C., Ried, L. D., et al. (2008). 'Metabolic monitoring in veterans with schizophrenia-related disorders and treated with second-generation antipsychotics: findings from a Veterans Affairs-based population.' *Journal of American Pharmacists Association* (2003) 48(3), 393–400.

Isaac, M. T. and Isaac, M. B. (2004). 'Consensus development conference on antipsychotic drugs and obesity and diabetes: response to consensus statement.' *Diabetes Care* 27(8), 2088; author reply 2089–2090.

Jori, A., Bernardi, D., et al. (1964). 'Chlorpromazine and Glucose Metabolism.' *International Journal of Neuropharmacology* 3, 553–558.

Kamran, A., Doraiswamy, P. M., et al. (1994). 'Severe hyperglycemia associated with high doses of clozapine.' *The American Journal of Psychiatry* 151(9), 1395.

Kesselheim, A. S. and Avorn, J. (2007). 'The role of litigation in defining drug risks.' *The Journal of the American Medical Association* 297(3), 308–311.

Ketter, T. A. and Haupt, D. W. (2006). 'Perceptions of weight gain and bipolar pharmacotherapy: results of a 2005 survey of physicians in clinical practice.' *Current Medical Research and Opinion* 22(12), 2345–2353.

Koller, E., Malozowski, S., et al. (2001). 'Atypical antipsychotic drugs and hyperglycemia in adolescents.' *The Journal of the American Medical Association* 286(20), 2547–2548.

Koller, E., Schneider, B., et al. (2001). 'Clozapine-associated diabetes.' *American Journal of Medicine* 111(9), 716–723.

Koller, E. A., Cross, J. T., et al. (2003). 'Risperidone-associated diabetes mellitus: a pharmacovigilance study.' *Pharmacotherapy* 23(6), 735–744.

Koller, E. A. and Doraiswamy, P. M. (2002). 'Olanzapine-associated diabetes mellitus.' *Pharmacotherapy* 22(7), 841–852.

Koller, E. A., Malozowski, S., et al. (2001). 'Atypical antipsychotic drugs and hyperglycemia in adolescents.' *The Journal of the American Medical Association* 286(20), 2547–2548.

Koller, E. A., Weber, J., et al. (2004). 'A survey of reports of quetiapine-associated hyperglycemia and diabetes mellitus.' *Journal of Clinical Psychiatry* 65(6), 857–863.

Kooy, F. H. (1919). 'Hyperglycaemia in mental disorders.' *Brain: A Journal of Neurology* 42, 214–283.

Koval, M. S., Rames, L. J., et al. (1994). 'Diabetic ketoacidosis associated with clozapine treatment.' *The American Journal of Psychiatry* 151(10), 1520–1521.

Lambert, B. L., Cunningham, F. E., et al. (2006). 'Diabetes risk associated with use of olanzapine, quetiapine, and risperidone in veterans health administration patients with schizophrenia.' *The American Journal of Epidemiology* 164(7), 672–681.

Lieberman, J. A., Stroup, T. S., et al. (2005). 'Effectiveness of antipsychotic drugs in patients with chronic schizophrenia.' *The New England Journal of Medicine* 353(12), 1209–1223.

Lilly, E. (2004). 'Lilly Expresses Concerns With Opinion of ADA Panelon Antipsychotic', Eli Lilly and Company.

Lindenmayer, J. P., Czobor, P., et al. (2003). 'Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics.' *The American Journal of Psychiatry* 160(2), 290–296.

Lopez-Munoz, F., Alamo, C., et al. (2005). 'History of the discovery and clinical introduction of chlorpromazine.' *Annals of Clinical Psychiatry* 17(3), 113–135.

Maglione, M., et al. (2011). 'Off-Label Use of Atypical Antipsychotics: An Update.' *Comparative Effectiveness Review*.

Marder, S. R., Essock, S. M., et al. (2002). 'The Mount Sinai conference on the pharmacotherapy of schizophrenia.' *Schizophrenia Bulletin* 28(1), 5–16.

Mauer, B. (2008). *Measurement of Health Status for People with Serious Mental Illnesses*, National Association of State Mental Health Program Directors.

McCarrick, A. K., Manderscheid, R. W., et al. (1986). 'Chronic medical problems in the chronic mentally ill.' *Hospital and Community Psychiatry* 37(3), 289–291.

Mefferd, R. B. Jr., Labrosse, E. H., et al. (1958). 'Influence of chlorpromazine on certain biochemical variables of chronic male schizophrenics.' *The Journal of Nervous and Mental Disease* 127(2), 167–179.

Meyer, J. M. (2001). 'Effects of atypical antipsychotics on weight and serum lipid levels.' *Journal of Clinical Psychiatry* 62, Suppl. 27, 27–34; discussion 40–21.

Meyer, J. M., Davis, V. G., et al. (2008). 'Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial: prospective data from phase 1.' *Schizophrenia Research* 101(1-3), 273–286.

Meyer: Personal Communication (2012).

MHRA (2002). Current Problems in Pharmacovigilance. *Olanzapine (Zyprexa) and Diabetes.* , Medicines and Healthcare products Regulatory Agency (MHRA), 28.

MHRA (2004). *Safety Warning: atypical antipsychotic drugs and stroke*.

MHRA (2005). *Safety Warning: new advice issued on risperidone and olanzapine.*

Mitchell, A. J., Delaffon, V., et al. (2012). 'Guideline concordant monitoring of metabolic risk in people treated with antipsychotic medication: systematic review and meta-analysis of screening practices.' *Psychological Medicine* 42(1), 125–147.

Morrato, E. H., Druss, B., et al. (2010). 'Metabolic testing rates in 3 state Medicaid programs after FDA warnings and ADA/APA recommendations for second-generation antipsychotic drugs.' *Archives of General Psychiatry* 67(1), 17–24.

Morrato, E. H., Newcomer, J. W., et al. (2009). 'Metabolic screening after the American Diabetes Association's consensus statement on antipsychotic drugs and diabetes.' *Diabetes Care* 32(6), 1037–1042.

Muller-Oerlinghausen, B. (1984). 'A short survey on untoward effects of fluperlapine.' *Arzneimittelforschung* 34(1A), 131–134.

Nasrallah, H. A., Meyer, J. M., et al. (2006). 'Low rates of treatment for hypertension, dyslipidemia and diabetes in schizophrenia: Data from the CATIE schizophrenia trial sample at baseline.' *Schizophrenia Research* 86(1-3), 15–22.

Nasrallah: Personal Communication (2012).

Newcomer, J. (May, 2011). *Magnitude and frequency of obesity, diabetes, and other metabolic disturbances among relevant patient populations: Introduction and scope of the problem*. Adipogenic and Metabolic Effects of Antipsychotic Drugs. , Nutrition Obesity Research Center, University of Alabama At Birmingham.

Newcomer, J. W. (2005). 'Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review.' *CNS Drugs* 19, Suppl. 1, 1–93.

Newcomer, J. W., Nasrallah, H. A., et al. (2004). 'The Atypical Antipsychotic Therapy and Metabolic Issues National Survey: Practice Patterns and Knowledge of Psychiatrists.' *Journal of Clinical Psychopharmacology* 24(5), S1–S6.

NICE (2010). *Core Interventions in the Treatment and Management of Schizophrenia in Adults in Primary and Secondary Care*, National Collaborating Centre for Mental Health.

Osser, D. N., Najarian, D. M., et al. (1999). 'Olanzapine increases weight and serum triglyceride levels.' *Journal of Clinical Psychiatry* 60(11), 767–770.

Petersen, T. J., Huffman, J. C., et al. (2008). 'Reach of benchmark psychiatric trial results to community-based providers: a case study of CATIE.' *Journal of Clinical Psychiatry* 69(7), 1081–1086.

Potter: Personal Communication (2012).

Pritchard, C. (2005). Eli Lilly agrees to Zyprexa settlement. *Market Watch*.

Raphael, T. and Parsons, J. (1921). 'Blood sugar studies in dementia praecox and manic-depressive insanity.' Archives of Neurology & Psychiatry 5(6): 687–709.

Rockoff, J. (2009). 'Antipsychotics Cause Weight Gain in Kids.' *Wall Street Journal*.

Rosenheck, R. L., Douglas, and Sernyak, M. (2001). 'From Clinical Trials to Real-World Practice: Use of Atypical Antipsychotic Medication Nationally in the Department of Veterans Affairs.' *Medical Care* 39(3), 302–308.

Safety Div./MHLW (2002). Press Release, Ministry of Health, Labour & Welfare (MHLW),16, 29.

Sasaki, J., Funakoshi, M., et al. (1985). 'Lipids and apolipoproteins in patients treated with major tranquilizers.' *Clinical Pharmacology and Therapeutics* 37(6), 684–687.

Sasaki, J., Kumagae, G., et al. (1984). 'Decreased concentration of high density lipoprotein cholesterol in schizophrenic patients treated with phenothiazines.' *Atherosclerosis* 51(2–3), 163–169.

Schmit, J. (2006). 'Bristol's $499m drug-pricing settlement among biggest.' *USA Today*.

Schwarz L. M. R., (1968). 'Blood sugar levels in patients treated with chloropromazine.' *The American Journal of Psychiatry* 125, 2523–2525.

Sheitman, B. B., Bird, P. M., et al. (1999). 'Olanzapine-induced elevation of plasma triglyceride levels.' *The American Journal of Psychiatry* 156(9), 1471–1472.

Shekelle P. E. A. (2007) 'Comparative Effectiveness of Off-Label Use of Atypical Antipsychotics.' *Comparative Effectiveness Review*.

Sobel, M., Jaggers, E. D., et al. (1999). 'New-onset diabetes mellitus associated with the initiation of quetiapine treatment.' *Journal of Clinical Psychiatry* 60(8), 556–557.

Suppes, T.,. McElroy, S. L., et al. (2007). 'Awareness of metabolic concerns and perceived impact of pharmacotherapy in patients with bipolar disorder: a survey of 500 US psychiatrists.' *Psychopharmacology Bulletin* 40(2), 22–37; quiz 38–40.

Taylor, N. (2010) 'FDA taking more cautious approach to non-inferiority trials.'

Thomas, W. J. (1999). 'Direct-to-Consumer Pharmaceutical Advertising: Catalyst for a Change in the Therapeutic Model in Psychotherapy?' *Connecticut Law Review* 32, 209.

Thonnard-Neumann, E. (1968). 'Phenothiazines and diabetes in hospitalized women.' *The American Journal of Psychiatry* 124(7), 978–982.

Tollefson, G. D. (1997). 'Practical Issues in Using Olanzapine.' *Journal of Clinical Psychiatry* 58(10), 73.

Tollefson, G. D., Beasley Jr., C. M., et al. (1997). 'Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial.' *The American Journal of Psychiatry* 154(4), 457–465.

Veterans Administration (2004). *Management of persons with psychoses*. Washington (DC), Department of Defense.

Watkins, K. E., Keyser, D. J., et al. (2010). 'Transforming mental healthcare in the Veterans Health Administration: a model for measuring performance to improve access, quality, and outcomes.' *Journal for Healthcare Qualilty* 32(6), 33–42; quiz 42–33.

Wilson, D. (2009). 'Weight Gain Associated With Antipsychotic Drugs'. *New York Times*.

Wilson, D. (2010). 'Side Effects May Include Lawsuits'. *New York Times*.

Winkelman, N. W., Jr. (1964). 'A Clinical and Socio-Cultural Study of 100 Psychiatric Patients Started on Chlorpromazine 20 and One Half Years Ago.' *The American Journal of Psychiatry* 120, 861–869.

Wirshing, D. A., Spellberg, B. J., et al. (1998). 'Novel antipsychotics and new onset diabetes.' *Biological Psychiatry* 44(8), 778–783.

WSJ (2003). Drug Debate: New Antipsychotics Pose a Quandary for FDA, Doctors. *Wall Street Journal*.

Young, A. S., Niv, N., et al. (2008). 'The Appropriateness of Routine Medication Treatment for Schizophrenia.' *Schizophrenia Bulletin*, sbn 138.

CHAPTER 7 Cognitive-enhancing drugs

7.1 Summary

In 1909, German psychiatrist Emil Kraepelin described the mental illness now known as schizophrenia as a disturbance of emotions and cognitive processes. Positive psychotic symptoms are the most evident and compelling manifestations of the illness, and they have been the target of the majority of available treatments. However, decades of research have contributed to a better understanding of the centrality of cognitive deficits to the psychopathology of schizophrenia, the anatomical and physiological brain correlates of these deficits, and their close association with poor functional outcomes.

Although important research on cognitive processes among hospitalised patients with schizophrenia was conducted in the 1930s in the US, cognition in schizophrenia received limited attention until antipsychotics were introduced in the 1950s, when US. researchers began investigating the potential cognitive effects of these drugs. This line of research has continued to this date; although some studies have reported positive effects, there is growing consensus that antipsychotics have little if any cognitive-enhancing effects. Between the 1970s and the 1990s, teams of investigators mainly based in the US worked on various lines of research related to brain abnormalities associated with cognitive deficits in people with schizophrenia. Although this early basic science research may have initially appeared somewhat disjointed, it laid the empirical foundation for later *research and development* (R&D) efforts on cognitive-enhancing (or pro-cognitive) drugs. By the mid 1990s, the field was ripe to embrace the findings of a seminal study that demonstrated the critical association between cognition and functioning in schizophrenia and thus provided the most important rationale for focusing on cognitive impairments as a treatment target.

The first concrete effort aimed at promoting research on cognitive-enhancing drugs for people with schizophrenia began in March 2001 with the *National Institute of Mental Health* (NIMH) decision to develop a programme aimed at facilitating drug development in this area. In 2003, the NIMH programme came to fruition with the launching of the *Measurement and Treatment Research to Improve Cognition in Schizophrenia* (MATRICS) initiative. Although MATRICS' goal was to construct a pathway to drug approval, the lack of a consensus battery to measure cognitive deficits made it necessary to concentrate efforts on the development of the *MATRICS Consensus Cognitive Battery* (MCCB). In April 2004, during a MATRICS-sponsored meeting convened to develop guidelines for the design of clinical trials of cognitive-enhancing drugs, the US *Food and Drug Administration* (FDA) made the controversial clarification that drug approval was contingent on concurrent change on a co-primary measure of functional outcome. A month later, NIMH funded the

Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) initiative, whose goal was to select and test potential cognitive-enhancing drugs. At the final MATRICS meeting held in September 2004, discussions focused on the need for research aimed at evaluating animal models for the MATRICS cognitive domains and at more precisely measuring cognition in schizophrenia drug discovery. These discussions paved the way for another NIMH-sponsored initiative, the *Cognitive Neuroscience Treatment to Improve Cognition in Schizophrenia* (CNTRICS). As reported in 2010, the MATRICS guidelines and the MCCB were adopted by several researchers in their studies of cognitive-enhancing drugs.

In January 2009, the European Commission approved funding for *Methods leading to New Medications in Depression and Schizophrenia* (NewMeds), a programme focused on the discovery of cognitive-enhancing and other psychiatric drugs. Described as a very unusual public–private collaboration, the primary goal of NewMeds is to improve preclinical–clinical translation.

7.2 Case study scope

This case study focuses on the recognition of the importance of cognitive deficits as a target for pharmacological treatment in schizophrenia, the development of more valid/reliable means to measure these deficits, and the development of cognitive-enhancing drugs. Secondarily, the case study examines research efforts aimed at understanding the cognitive effects of currently available antipsychotic drugs.

7.3 Glossary

Akathisia: a condition marked by restlessness and inability to sleep or relax that may be observed with antipsychotic drug treatment.

Anticholinergic drugs: medications used to control extrapyramidal symptoms induced by certain antipsychotic drugs (those with high affinity for dopamine receptors).

Antipsychotic drugs: medications used to control psychotic symptoms. Two classes of antipsychotic drugs exist: first-generation (or conventional) and second-generation (or atypical). This classification is based on their mechanism of action. However, while all first-generation antipsychotics were developed between the 1950s and the 1980s, all second-generation antipsychotics, with the exception of clozapine (developed in 1959), were developed since the 1990s.

Chlorpromazine: first *first-generation antipsychotic*

Clozapine: first *second-generation antipsychotic*

Cognitive domains: fundamental dimensions of cognitive deficit in schizophrenia that may be assessed as separable cognitive functions. Domains assessed by the MATRICS Consensus Cognitive Battery include Speed of Processing; Attention/Vigilance; Working Memory; Verbal Learning and Memory; Visual Learning and Memory; Reasoning and Problem Solving; and Social Cognition. Verbal Comprehension, also a cognitive domain, was not included in the cognitive battery due to its resistance to change.

Cognitive remediation: a non-pharmacological psychosocial intervention that seeks to improve cognitive functioning of persons with schizophrenia. It employs a variety of methods, including drill and practice exercises, teaching strategies, compensatory strategies to reduce the effects of persistent cognitive impairments, and group discussions.

Co-primary Measure (of cognitive outcome): outcome measure for pro-cognitive drug R&D that assesses drug effects on functioning; needs to be assessed along with the primary measure (drug effects on cognitive performance assessed through tests).

Dorsolateral prefrontal cortex: brain region associated with executive function.

Executive function: a term that describes the mental processes that regulate and control cognitive functions such as memory, planning, attention and problem solving.

Extrapyramidal Symptoms: involuntary movements reflecting abnormal extrapyramidal function that may be observed with antipsychotic drug treatment. These include acute dystonic reactions, parkinsonism and akathisia.

Glycinergic agent: pharmacological agent acting at the glycine site of the *N-methyl-d-aspartic acid* (NMDA) glutamatergic receptors.

Negative psychotic symptoms: category of psychotic symptoms characterised by the absence or loss of experience. Negative psychotic symptoms include decrease in emotional responsiveness; decrease in verbal production; and decrease in motivation or follow through.

Neuropsychological Deficits: psychological function deficits closely linked to the function of particular areas, neural pathways or cortical networks in the brain.

Positive psychotic symptoms: category of psychotic symptoms characterised by an excess or distortion of the individual's normal functioning. These include delusions (false beliefs that are firmly held) and hallucinations (seeing, hearing, feeling, smelling or tasting something that is not actually there).

Psychomotor: pertaining to both the psychological and motoric realms (ie intrapsychic and behavioral).

Psychopathology: the study of the origin, development, and manifestations of mental or behavioral disorders.

Tardive Dyskinesia: neurological disorder resulting in involuntary, repetitive body movements that may result from prolonged antipsychotic drug treatment.

Treatment-refractory: resistant to conventional treatment.

7.4 Acronyms

CATIE: Clinical Antipsychotic Trials of Intervention Effectiveness

CNTRICS: Cognitive Neuroscience Treatment to Improve Cognition in Schizophrenia

DLPFC: Dorsolateral Prefrontal Cortex

EUFEST: European First Episode Schizophrenia Trial

FDA: US Food and Drug Administration

FGA: first-generation antipsychotic

MATRICS: Measurement and Treatment Research to Improve Cognition in Schizophrenia

MCCB: MATRICS Consensus Cognitive Battery

NIMH: National Institute of Mental Health

PORT: Patient Outcomes Research Team

R&D: research and development

SGA: second-generation antipsychotic

TURNS: Treatment Units for Research on Neurocognition and Schizophrenia

UPSA: UCSD Performance Based Skills Assessment

VIM: Validation of Intermediate Measures

7.5 Timeline of key events

Key:

US
UK
Canada
International

Year	Event
1909	Emil Kraepelin postulates that several psychotic conditions are part of a single disease entity named dementia praecox (now known as schizophrenia, a term coined by Eugen Bleuler). He described the condition as a disturbance of emotional and cognitive processes (including attention, memory, and "mental efficiency") that began early in life and had a deteriorating course (Kraepelin 1919; Kraepelin 1987).
1937	Altman and Shakow publish in the Journal of Educational Psychology the first of a series of studies on intelligence, thinking, and memory, conducted at the Worcester State Hospital between 1927 and 1946 (Altman and Shakow 1937). The study showed that people with schizophrenia performed worse on a test of 'thinking disturbance'.
1939	Cameron publishes a paper in the Journal of Abnormal and Social Psychology entitled 'Deterioration and regression in schizophrenic thinking', where he posits that over-inclusive thinking is at the core of disordered thinking in schizophrenia (Cameron 1939).
1958	The Journal of Consulting Psychology publishes a study that assessed

	chlorpromazine's effects on the learning process and on verbalised social adaptation in a group of hospitalised chronic psychotic patients (Whitehead and Thune 1958). The authors found that chlorpromazine 'does not significantly affect the learning process, but does have influence on motivation'.
1961	The Journal of Abnormal and Social Psychology reports on a placebo-controlled study that used a word association task to assess the effect of chlorpromazine on learning (Vestre 1961). The author concluded that chlorpromazine affected 'learning and retention negatively''.
1964	The Journal of Neuropsychiatry publishes one of the earliest studies that assessed whether performance on neurocognitive tests predicted acquisition of psychosocial skills needed for community functioning (Weaver and Brooks 1964). The study showed that patients with schizophrenia exhibited significant slowness on a variety of psychomotor tests.
1968	The Journal of Experimental Research in Personality publishes the first randomised controlled trial (RCT) of cognitive remediation in schizophrenia, conducted among inpatients (Wagner, in McGurk, Twamley et al. 2007). The author found that noncomputerised attention training led to substantial improvements in visual learning memory, reasoning and problem solving.
1976	Lancet publishes a study that showed increased cerebral ventricular size among 17 institutionalised patients with schizophrenia relative to age-matched employed controls (Johnstone, Crow et al. 1976). Within the group of patients with schizophrenia, increased ventricular size was significantly related to indices of cognitive impairment.
1978	The Journal of Clinical Psychology publishes a paper reporting on neuropsychological impairment in schizophrenic patients relative to 25 normal controls (Heaton, Vogt et al. 1979). The study found that neuropsychological impairment had a higher correlation with degree of EEG abnormality than with degree of psychosis, suggesting a possible organic basis for the deficits exhibited by patients.
April 1982	The Journal of Psychiatric Research publishes a paper entitled 'Schizophrenia: Caused by a fault in programmed synaptic elimination during adolescence?' (Feinberg 1982). The author posited that 'abnormal rates of programmed cell elimination occurring during adolescence contribute to the development of cognitive impairment and psychotic symptoms associated with schizophrenia' (Lesh, Niendam et al. 2011).
1984	Psychological Medicine publishes a study that compared verbal recall and recognition among normal controls and patients with schizophrenia on antipsychotic drugs alone or co-prescribed with anticholinergic medications (Calev 1984). The author found that patients with schizophrenia taking both classes of drugs performed

	worst on cognitive tests.
February 1986	Archives of General Psychiatry publishes the first of several studies that simultaneously evaluated dorsolateral prefrontal cortex (DLPFC) physiology and function among patients with schizophrenia, and generated evidence of physiologic dysfunction (Weinberger, Berman et al. 1986).
July 1987	Archives of General Psychiatry publishes a paper proposing that the development of symptoms of schizophrenia is the end result of an early developmental pathology, particularly in the DLPFC, affecting normal brain maturational events occurring much later (Weinberger 1987).
November 1987	Archives of General Psychiatry publishes a paper that reported on a study that investigated the potential reversibility of cognitive deficits and the role of state variables such as attention and motivation among patients with schizophrenia (Goldberg, Weinberger et al. 1987).
1987	Stephen Stahl, a psychopharmacology researcher then-affiliated with Merck Sharp & Dome Research Laboratories, publishes a paper entitled 'Needs and opportunities for innovation in psychopharmacology' (Stahl 1987). Among the author's wish list for psychopharmacological innovations were agents to alleviate cognitive failure for schizophrenia.
1989	The Journal of Abnormal Psychology publishes a review of research that examined the influence of antipsychotic and anticholinergic drugs on cognitive processes in schizophrenia (Spohn and Strauss 1989). The authors concluded that use of antipsychotic drugs is associated with limited normalisation on many psychological measures, whereas anticholinergics appear to disrupt some aspects of memory.
March 1990	Schizophrenia Bulletin publishes a review of the literature from the 1950s to the late 1980s on the effects of first generation antipsychotics (FGAs) on perceptual and neuropsychological function in patients with chronic schizophrenia (Cassens, Inglis et al. 1990).
November 1990	Archives of General Psychiatry publishes a paper reporting on a study that assessed 16 pairs of monozygotic twins discordant for schizophrenia on a wide range of neuropsychological tests (Goldberg, Ragland et al. 1990). The authors found that the affected twins tended to perform worse than their unaffected counterparts on most of the tests. They concluded that neuropsychological dysfunction may be a consistent feature of schizophrenia and that it is related primarily to the clinical disease process and not to genetic or nonspecific environmental factors.
1991	Science publishes a study that indicated that D1 dopamine receptors located in the prefrontal cortex are involved in working memory

	(Sawaguchi and Goldman-Rakic 1991).
May 1992	British Journal of Psychiatry publishes a study on the effects of clozapine among treatment-resistant patients with schizophrenia (Meltzer 1992). The author found significant improvement in several domains, including some types of cognitive function. The author emphasised the need to assess independent medication effects in multiple domains, including cognitive functioning.
January 1993	British Journal of Psychiatry publishes a study on the cognitive effects of clozapine (Goldberg, Greenberg et al. 1993). The authors found that although psychiatric symptoms improved, cognitive functions were essentially unchanged, and that cognitive disability was rate-limiting in the sample's functional rehabilitation.
November 1993	Biological Psychiatry publishes a study which assessed cognitive functions and psychopathology in treatment-refractory patients with schizophrenia before initiation of clozapine, and at follow-up (Hagger, Buckley et al. 1993). At follow-up, researchers found improvement in measures of retrieval from reference memory and in some tests of executive function, attention, and recall memory.
February 1994	Archives of General Psychiatry publishes a study that sought to differentiate 'primary (neuropsychological) deficits from changes secondary to medication or chronicity' (Saykin, Shtasel et al. 1994). The authors concluded that verbal memory is a primary neuropsychological deficit present early in the course of schizophrenia.
November 1994	Journal of Neuropsychiatry and Clinical Neurosciences publishes a paper in which the author asserted that a robust body of evidence supports the theory that a defect in working memory 'may be the fundamental impairment leading to schizophrenic thought disorder' (Goldman-Rakic 1994).
December 1994	Biological Psychiatry publishes the first controlled study assessing the cognitive effects of clozapine (Buchanan, Holstein et al. 1994). Authors found short- and long-term advantages for clozapine, concluding that long-term clozapine treatment may have beneficial effects on a broad range of cognitive functions.
September 1995	Schizophrenia Research publishes a paper reporting on a study that assessed monozygotic twin pairs (discordant and concordant for schizophrenia, as well as normal twin pairs) to study cognitive measures of genetic risk in schizophrenia (Goldberg, Torrey et al. 1995). Although authors found subtle attenuation in some cognitive variables in the unaffected twins compared to normal twins, large differences between unaffected and affected members of discordant pairs on a wide variety of cognitive variables highlighted the magnitude of disease-specific factors.
1996	The American Journal of Psychiatry publishes a review paper aiming to determine 'which, if any, neurocognitive deficits restrict the

	functioning of patients with schizophrenia in the outside world' (Green 1996). The author found that various cognitive deficits were predictive of functional outcomes whereas (positive) psychotic symptoms were not.
1997	Schizophrenia Bulletin publishes a paper where authors 'recount efforts to dissect the cellular and circuit basis of working memory with the goal of extending the insights gained from the study of normal brain organization in animal models to an understanding' of schizophrenia (Goldman-Rakic and Selemon 1997).
1998	Neuropsychology publishes a meta-analysis of the neurocognitive literature on test performance in schizophrenia (Heinrichs and Zakzanis 1998). Results of the meta-analysis indicated that 'schizophrenia is characterized by a broadly based cognitive impairment with varying degrees of deficit in all ability domains measured by standard clinical tests.'
February 2001	The American Journal of Psychiatry publishes a review of studies on drug-mediated cognitive enhancement (Harvey and Keefe 2001). The authors conclude that although second generation antipsychotics (SGAs) 'appear to have preliminary promise for the enhancement of cognitive functioning […], the methodology for assessing the treatment of cognitive deficits is still being developed'.
March 2001	Plans to develop a programme in treatment development by the Director of the National Institute of Mental Health (NIMH) leads to the selection of cognitive impairment as a new target and a request for proposals to address some of the important obstacles in drug development in this area.
Spring 2001	Schizophrenia Bulletin reports on a 'new measure of everyday functioning for severely mentally ill adults' named UCSD Performance Based Skills Assessment (UPSA) (Patterson, Goldman et al. 2001).
October 2001	The Journal of Clinical Psychopharmacology publishes a pilot study that found that augmentation of clozapine with an experimental glutamate-stimulating compound resulted in improvement in memory and attention (Goff, Leahy et al. 2001). However, a larger study that added the same compound to clozapine, olanzapine, and risperidone failed to replicate this earlier finding.
2002	Science publishes a paper that serves as a key contribution to the re-conceptualisation of schizophrenia as a syndrome with multiple domains of dysfunction, rather than as a single illness with one diagnosis, one treatment and an explanatory pathophysiology (Hyman and Fenton 2003).
2003	The NIMH-funded contract to UCLA launches the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative. Its goals are 'to identify the most promising

	science-based ideas regarding the neurochemical basis of (cognitive) deficits, and to achieve a broad academic, industry, and regulatory agreement on the best way to measure cognition in clinical trials'.
April 2003	NIMH convenes academic, industry and regulatory experts under the MATRICS initiative to review available data and create a consensus battery specifically designed to assess cognitive impairments in schizophrenia (first MATRICS consensus conference). The battery is eventually named MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein, Barch et al. 2004).
April 2004	MATRICS investigators organise a consensus meeting sponsored by the US Food and Drug Administration (FDA) and NIMH to develop recommendations for subject selection, co-primary outcome measures, and statistical approaches for study design. At the meeting, the FDA clarified that 'approval of a neurocognitive drug for schizophrenia' was contingent on 'concurrent change on a co-primary measure of functional outcome'.
May 2004	NIMH awards a four-year contract to UCLA and five other academic medical centres to create a network of Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) aimed at selecting and testing potential cognitive-enhancing agents (PI: Stephen Marder).
September 2004	The final MATRICS meeting ('New Approaches Conference') aims to develop a research agenda to address scientific issues identified through the MATRICS process, which eventually leads to the Cognitive Neuroscience Treatment to Improve Cognition in Schizophrenia (CNTRICS) initiative (Carter and Barch 2007; Stover, Brady et al. 2007; Geyer 2010).
2004	Biological Psychiatry publishes a meta-analysis of studies that compared cognitive effects of FGAs versus placebo or no medication among patients with schizophrenia. Authors found modest-to-moderate gains in multiple cognitive domains (Mishara and Goldberg 2004).
February 2007	First of three meetings of the completed first round of CNTRICS. CNTRICS II, also completed, held four meetings (October 2009 – April 2011).
February 2007	Obstacles in drug development lead to the formation of MATRICS CT (Coprimary selection and Translation of the MCCB), an NIMH programme led by Stephen Marder and Brendon Binneman, and supported through donations of a partnership of pharmaceutical companies to the Foundation at NIMH.
June 2007	Archives of General Psychiatry publishes a study based on the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), the aim of which was to compare the neurocognitive effects of Phase I antipsychotics (perphenazine, an FGA, and four SGAs) (Keefe, Bilder

	et al. 2007). The authors found that two months into the study, all groups had a small but significant improvement in neurocognition.
October 2007	American Journal of Psychiatry publishes a paper reporting on the results of a study that assessed the effects of glycinergic agents on negative symptoms and cognitive functions in patients with schizophrenia (Buchanan, Javitt et al. 2007). The authors found that neither of the agents used in the trial were 'generally effective therapeutic options for treating negative symptoms or cognitive impairments'.
January 2009	The European Commission approves funding for preclinical-clinical translation research under the program Novel Methods Leading to New Medications in Depression and Schizophrenia (NewMeds), part of the Innovative Medicines Initiative. Funds were set aside for a programme on psychiatric drug discovery, including drugs to treat the cognitive impairments associated with schizophrenia (Geyer 2010).
June 2009	The American Journal of Psychiatry publishes results from the European First Episode Schizophrenia Trial (EUFEST), an industry-funded open-label RCT (N= 498) (Davidson, Galderisi et al. 2009). The authors concluded that 'treatment with antipsychotic medication (haloperidol, an FGA, and four SGAs) is associated with moderate improvement in the cognitive test performance'.
June 2009	In an editorial accompanying the EUFEST study, Terry Goldberg states that practice effects and other factors need to be considered when evaluating the positive findings of both CATIE and EUFEST (Goldberg and Gomar 2009).
January 2010	Schizophrenia Bulletin publishes the 2009 Schizophrenia Patient Outcomes Research Team (PORT) psychopharmacological treatment recommendations and summary statements (Buchanan, Kreyenbuhl et al. 2010). PORT researchers stated that there is 'little evidence that [FGAs and SGAs] have significant cognitive-enhancing effects', adding that 'there is currently insufficient evidence to support the use of any adjunctive agent for the treatment of cognitive impairments in people with schizophrenia'.
2010	Several pharmaceutical companies. including AstraZeneca, GlaxoSmithKline and Sanofi, announce that they will stop conducting schizophrenia research in a drive to focus R&D efforts and cut costs.
2010	Schizophrenia Bulletin publishes a paper where MATRICS investigators and the Director of the FDA's Psychiatry Products Division review studies that have examined the effect of pharmacological interventions on cognitive performance (Buchanan, Kreyenbuhl et al. 2010). They reported that many of those studies had used the FDA-NIMH-MATRICS guidelines as well as MCCB. Among the completed studies, two were TURNS trials and two were

	industry-sponsored.
February 2011	Archives of General Psychiatry publishes results of a longitudinal study of treated patients with schizophrenia followed with serial MRI (Ho, Andreasen et al. 2011). The authors found that the amount of exposure to antipsychotic medication predicted decrements in cerebral grey and white matter volumes and increased the volume of the putamen.
February 2011	In an editorial commenting on the findings by Ho and colleagues, David Lewis wondered if reductions in brain volume associated with antipsychotic medications impair function, or if they are related to the therapeutic benefits of these medications (Lewis 2011). He could not discount, however, that as suggested by Ho and colleagues, antipsychotics may 'improve symptoms and contribute to progressive brain tissue reductions through different actions on separate brain circuits'.
March 2011	Biological Psychiatry publishes a TURNS-sponsored RCT that assessed outcomes of a GABA partial agonist for the treatment of cognitive impairments in patients with schizophrenia (Buchanan, Keefe et al. 2011). The authors did not find group differences on the main outcome measure (MCCB) or the co-primary functional measures.
April 2011	The American Journal of Psychiatry publishes a paper written by MATRICS investigators reporting on the MATRICS-CT-sponsored Validation of Intermediate Measures (VIM) study, which aimed to validate co-primary measures (Green, Schooler et al. 2011). Their findings led the VIM Committee to consider UPSA as the leading co-primary measure.
May 2011	The American Journal of Psychiatry publishes a meta-analysis of studies of cognitive remediation therapy for schizophrenia published up to June 2009 (Wykes, Huddy et al. 2011). The authors concluded that 'cognitive remediation benefits people with schizophrenia, and when combined with psychiatric rehabilitation, this benefit generalises to functioning, relative to rehabilitation alone'.

7.6 Narrative

In 1909, German psychiatrist Emil Kraepelin presented a landmark paper entitled 'The Diagnosis and Prognosis of Dementia Praecox', in which he postulated that several psychotic conditions were part of a single disease entity. He described the condition as a disturbance of emotional and cognitive processes (including attention, memory and 'mental efficiency'), that began early in life and had a deteriorating course (Kraepelin 1987). Although he named it dementia praecox, the condition is now known as schizophrenia, a term coined by Eugen Bleuler.

For the next several decades, however, attention to cognitive processes in schizophrenia was scarce and patchy.

In 1937, Charlotte Hall Altman and David Shakow published the first of a series of studies on intelligence, thinking and memory conducted at the Worcester State Hospital in Massachussetts between 1927 and 1946 as part of an ambitious research programme on schizophrenia (Altman and Shakow 1937). Shakow was cited by Terry Goldberg, Anthony David and James Gold as a pioneer in the conduct of empirical research that eventually cemented the view that impairments in cognition are central to schizophrenia (Goldberg et al. 2011). In 1938, Norman Cameron at Cornell Medical College, published a paper entitled 'Deterioration and regression in schizophrenic thinking' in which he posited that 'overinclusive thinking' is at the core of disordered thinking in schizophrenia (Cameron 1939). According to Spohn and Strauss, this theory generated a good deal of research in the 1950s and 1960s, including some studies of the cognitive effects of antipsychotics (Spohn and Strauss 1989).

Following the introduction of antipsychotics in the 1950s, researchers began looking at the potential cognitive effects of these drugs. A paper published in 1958 reported on a randomised placebo-controlled trial that assessed chlorpromazine's effects on different aspects of the learning process and on verbalised social adaptation in a group of hospitalised chronic psychotic patients (Whitehead and Thune 1958). The authors found that chlorpromazine 'does not significantly affect the learning process', but they found it dampens motivation. They concluded that their study provided support to the hypothesis that 'motivation is a key factor in learning deficit found in psychotic groups.' However, another placebo-controlled trial published in 1961 that used a word association task to assess the effect of chlorpromazine on learning, concluded that chlorpromazine negatively affected learning and retention (Vestre 1961). This pattern of mixed findings on the cognitive effects of antipsychotics has been a constant throughout the decades for this line of research.

Two important non-pharmacological research developments occurred in the 1960s. In 1964, researchers published the results of a study showing that neurocognitive test performance (psychomotor speed) predicted selection for rehabilitation programmes (Weaver and Brooks 1964). This is the earliest study selected by Michael Green for his landmark review of evidence on the association between cognitive deficits and functioning in persons with schizophrenia (Green 1996). The results of the first *randomised controlled trial* (RCT) on the effectiveness of a psychosocial intervention for cognitive deficits in schizophrenia (cognitive remediation), published in 1968, showed that non-computerised attention training leads to substantial improvements in visual learning memory and reasoning and problem solving (Wagner, in (McGurk, Twamley et al. 2007).

Evidence on the anatomical correlates of cognitive deficits began to emerge in the 1970s. In 1976, UK researchers published a study showing increased cerebral ventricular size among institutionalised patients with schizophrenia relative to age-matched employed controls (Johnstone, Crow et al. 1976). A key conclusion of this study was that increased ventricular size was highly significantly related to indices of cognitive impairment; this study did not elucidate the mechanisms underlying this association. In 1978, researchers performed detailed neuropsychological evaluations of recently hospitalised persons with

schizophrenia in whom neurologic work-ups had failed to reveal central nervous system disease (Heaton, Vogt et al. 1979). The authors found that neuropsychological impairment had a higher correlation with degree of electro-encephalographic abnormality than with degree of psychosis, suggesting a possible organic basis for their cognitive deficits. This has been considered a seminal study because as a result of the influence of psychoanalysis on schizophrenia diagnosis, the prevailing notion at the time was that organicity had to be ruled out prior to making a diagnosis of schizophrenia (Jaeger: Personal Communication 2012).

In 1982, Irwin Feinberg at the University of California at San Francisco, published a paper entitled 'Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence?' (Feinberg 1982). This paper has been described as an important conceptual contribution because the author 'introduced the highly influential "pruning" hypothesis of schizophrenia, which suggests that abnormal rates of programmed cell elimination occurring during adolescence contributes to the development of cognitive impairment and psychotic symptoms associated with schizophrenia' (Lesh, Niendam et al. 2011).

In 1984, Avraham Calev,[9] at the University of Manchester, published a study that compared verbal recall and recognition among normal controls and persons with schizophrenia on antipsychotic drugs alone or co-prescribed with anticholinergic medications, and found that regardless of medication status, persons with schizophrenia had the worst performance on cognitive tests (Calev 1984). This was an important study because it revisited the notion that cognitive deficits are a primary phenomenon of the schizophrenic illness.

Influential work on the association between cortical dysfunction and cognitive deficits in people with schizophrenia began to emerge in the 1980s. In 1986, Daniel Weinberger and other colleagues affiliated with the US *National Institute of Mental Health* (NIMH) published the first of four studies that simultaneously evaluated physiology and function of the *dorsolateral prefrontal cortex* (DLPFC) among medication-free patients with chronic schizophrenia and normal controls (Weinberger, Berman et al. 1986). The authors found that physiologic dysfunction in the DLPFC correlated with cognitive function. In July 1987, Daniel Weinberger published a widely cited paper proposing that the development of symptoms of schizophrenia is the end result of an early developmental pathology affecting the normal maturation of several brain areas, particularly the DLPFC, which occurs much later (Weinberger 1987). In the author's view, this was an important paper because it introduced the hypothesis that schizophrenia is a neurodevelopmental disorder, setting up the stage for all subsequent work related to this paradigm (Weinberger: Personal Communication 2011). Further, because of the importance of DLPFC for cognitive development, this paper provided critical support to the view that cognition is a central phenomenon of the illness (Weinberger: Personal Communication 2011). Later that year, the same group published a paper entitled 'Further evidence for dementia of the pre-frontal type in schizophrenia?' which reported on a study that investigated whether cognitive deficits among patients with schizophrenia could be reversed and whether

[9] This was soon after Calev completed his doctoral thesis at the University of York; this work closely related to/stemmed from experiments conducted with his doctoral research.

attention and motivation moderated cognitive performance (Goldberg, Weinberger, et al. 1987). They found no evidence of reversibility of prefrontal-type cognitive deficits. In the view of Daniel Weinberger, this paper was influential 'because it established that cognitive deficits of the prefrontal-type [are not] epiphenomena of ongoing psychosis', a common belief at the time (Weinberger: Personal Communication 2011).

The first public call for the development of a cognitive enhancement drug for patients with schizophrenia was published in 1987. Stephen Stahl, US-trained but then Executive Director of Clinical Neurosciences at the Merck Neuroscience Research Center in the UK, published a paper entitled 'Needs and opportunities for innovation in psychopharmacology' (Stahl 1987). The author's wish list for psychopharmacological innovations included agents to improve cognitive performance for Alzheimer's dementia, dementia praecox (schizophrenia), and other neuropsychiatric disorders.

New evidence on the cognitive effects of antipsychotics and other medications used to treat patients with schizophrenia emerged in the late 1980s. A review paper published in 1989 that examined a large body of research on the influence of antipsychotic and anticholinergic drugs on cognitive processes in schizophrenia concluded that use of antipsychotic drugs was associated with limited normalisation (modest improvement) on many psychological measures, whereas anticholinergics appeared to disrupt some aspects of memory (Spohn and Strauss 1989). In March 1990, researchers published another review of studies published between the 1950s and the late 1980s on the perceptual and neuropsychological effects of antipsychotics in patients with chronic schizophrenia (Cassens, Inglis et al. 1990). The authors found evidence 'that acute administration (…) impairs performance on some, but not all, tasks requiring vigilance and attention, and on some tasks requiring motor behavior.' In terms of chronic administration, the authors reported that antipsychotics 'improve performance on some tasks requiring sustained attention and visuomotor problem-solving skills' (depending on dose and length of administration), adding that 'consistent evidence' suggested that chronic administration does not impair neuropsychological function independent of motor function.

Research designed to examine the contribution of genetic endowment to cognitive deficits began to emerge in the early 1990s. In November 1990, Terri Goldberg and other NIMH-affiliated colleagues published the results of a study that assessed 16 pairs of monozygotic twins discordant for schizophrenia on a wide range of neuropsychological tests (Goldberg, Ragland et al. 1990). The authors found that the affected twins tended to perform worse than their unaffected counterparts on most of the tests. Because the deficits were especially severe on tests of vigilance, memory and concept formation, they posited that diffuse cortical dysfunction may be greatest in the frontotemporal cortex. In addition, the authors found that while psychiatric symptoms were not highly associated with neuropsychological scores, a global measure of social and vocational functioning was. They concluded that neuropsychological dysfunction may be a consistent feature of schizophrenia and that it is related primarily to the clinical disease process and not to genetic or nonspecific environmental factors. The importance of this paper is that it showed that 'no matter how well patients perform, they are relatively impaired compared to their genetic endowment (ie, their identical unaffected twin)' (Weinberger: Personal Communication 2011).

A study by Patricia Goldman-Rakic and colleagues published in 1991 reported that D1 dopamine receptors located in the prefrontal cortex are involved in working memory (Sawaguchi and Goldman-Rakic 1991). According to Cameron Carter and Deanna Barch, 'seminal work' by Goldman-Rakic and other researchers (Goldman-Rakic 1995; Goldman-Rakic, Muly et al. 2000) 'generated a wealth of information about the neural circuits and neurotransmitters that support working memory,' laying a critical foundation for targeted development of pro-cognitive drugs in schizophrenia (Carter and Barch 2007).

A 1992 paper by Herbert Meltzer reporting on a study of clozapine's effects in treatment-resistant patients with schizophrenia was important not so much for its contribution to the growing yet mixed evidence base on cognitive effects of antipsychotics, but because of its conceptual contribution (Meltzer 1992). The author reported on multiple outcome domains in addition to positive and negative symptoms and adverse effects, including cognitive function and quality of life. In the view of Robert Buchanan, a physician scientist who along with other researchers interviewed for this case study has played a key role formulating and developing a research agenda centered on schizophrenia's cognitive deficits, this paper is important because it called for a multidimensional perspective in the assessment of schizophrenia-related outcomes, prodding the field to assess areas of dysfunction that until then, had received little attention (Buchanan: Personal Communication 2012).

Further mixed evidence on the cognitive effects of antipsychotics emerged from four important studies published in 1993–1994. In January 1993, Terri Goldberg and NIMH-affiliated colleagues published the results of a non-controlled study that assessed psychiatric symptoms and cognitive functions in patients with schizophrenia, first while receiving *first-generation antipsychotics* (FGAs) and again after receiving clozapine (Goldberg, Greenberg et al. 1993). The authors found that although psychiatric symptoms improved in all patients, attention, memory and higher-level problem-solving were essentially unchanged, and that cognitive disability was rate-limiting in the sample's functional rehabilitation. They attributed the clozapine-related decline in some memory functions to the drug's potent anticholinergic properties. A paper published in 1993 reported on the results of another non-controlled study that assessed psychopathology and cognitive functions in treatment-refractory schizophrenic patients before initiation of clozapine, and at follow up (Hagger, Buckley et al. 1993). At follow up, researchers found improvement in measures of retrieval from reference memory and in some tests of executive function, attention, and recall memory, as well as some evidence for a relationship between improvement in psychopathology and cognitive function. In February 1994, researchers published a study that sought to differentiate 'primary (neuropsychological) deficits from changes secondary to medication or chronicity' by comparing antipsychotic-naïve patients suffering their first episode of schizophrenia with unmedicated but previously treated patients and healthy controls (Saykin, Shtasel et al. 1994). The authors found that the patient groups had nearly identical profiles showing generalised impairment, yet some functions not typically implicated in schizophrenia (spatial cognition, fine motor speed and visual memory) were more impaired in the previously treated group. They concluded that verbal memory is a primary neuropsychological deficit present early in the course of schizophrenia. The first study using a controlled design to assess the cognitive effects of clozapine was published in December 1994 (Buchanan, Holstein et al. 1994). The authors found that clozapine was

better than haloperidol, an FGA, in two measures of cognitive function at the end of the 10-week trial, and found a broader range of improved cognitive functioning at the end of one year of open treatment. They concluded that long-term clozapine treatment may have beneficial effects on a broad range of cognitive functions.

In late 1994, Patricia Goldman-Rakic summarised the state of the evidence on the importance of working memory dysfunction in schizophrenia. She wrote that 'studies of animals and of cognitive function in normal, brain-injured, and schizophrenic subjects support the theory that a defect in working memory – the ability to guide behavior by representations – may be the fundamental impairment leading to schizophrenic thought disorder' (Goldman-Rakic 1994).

New insights on the cognitive deficits in schizophrenia emerged in the fall of 1995 with the publication of another study by Terri Goldberg and NIMH-affiliated colleagues using a twin study research design to study cognitive measures of genetic risk in schizophrenia (Goldberg, Torrey et al. 1995). The authors assessed three sets of monozygotic twin pairs, one set discordant and the other concordant for schizophrenia, as well as normal twin pairs. A comparison between the unaffected twins from the discordant sample and the normal twins indicated subtle attenuations in some aspects of memory and executive functioning in the unaffected group, thus providing evidence for cognitive markers of a genetic component in schizophrenia. However, large differences between unaffected and affected members of discordant pairs on a wide variety of cognitive variables, including IQ, attention, memory and executive function, highlighted the magnitude of disease-specific factors. Further, in both the concordant and discordant groups, intra-pair differences in cognitive performance were powerful predictors of global level of social, vocational and interpersonal functioning. In the view of Daniel Weinberger, the importance of this study is that it showed that 'in monozygotic twins, both of whom have illness, the entire variance in outcome, social and vocational, was determined by differences in cognitive function (thus constituting) the first modern paper about the role of cognitive deficits on disability and outcome' (Weinberger: Personal Communication 2011).

In 1996, Michael Green published a seminal review of seventeen studies that had used 'neurocognitive measures as predictors or correlates of functional outcome for chronic schizophrenics (with the objective of) determining which, if any, neurocognitive deficits restrict the functioning of schizophrenic patients in the outside world' (Green 1996). The author found that various cognitive deficits were predictive of functional outcomes, including social outcome, vocational outcome, and success in rehabilitation programs, whereas – surprisingly in his view – psychotic symptoms were not. Terry Goldberg, Anthony David and James Gold referred to this study as influential because it was the first one to demonstrate the critical association between cognition and functioning in schizophrenia (Goldberg et al., 2011), which according to Stephen Marder, 'is the most important rationale for focusing on cognitive impairments as a treatment target' (Marder and Fenton 2004). Michael Green's motivations to undertake this study included the growing consensus that capacity for rehabilitation was not associated with positive or negative symptoms, growing disillusionment with antipsychotics' ability to improve functioning, and some evidence that cognition broadly defined was associated with psychosocial functioning.

Work on the neural circuits and neurotransmitters supporting working memory had proceeded throughout the 1990s. In 1997, Patricia Goldman-Rakic and a co-author published a paper entitled 'Functional and Anatomical Aspects of Prefrontal Pathology in Schizophrenia' where the authors 'recount efforts to dissect the cellular and circuit basis of working memory with the goal of extending the insights gained from the study of normal brain organization in animal models to an understanding' of schizophrenia (Goldman-Rakic and Selemon 1997).

The neurocognitive literature on test performance in schizophrenia was the subject of an influential research synthesis undertaken by Canadian researchers and published in 1998 (Heinrichs and Zakzanis 1998). The authors concluded that 'schizophrenia is characterized by a broadly based cognitive impairment, with varying degrees of deficit in all ability domains measured by standard clinical tests.' This study was described by Terry Goldberg, Anthony David and James Gold as an influential meta-analysis because it pointed to the need to broaden research attention beyond executive function and episodic memory dysfunction (Goldberg et al. 2011).

A review of the evidence on antipsychotics' cognitive effects undertaken by two prominent cognitive researchers was published in February 2001 (Harvey and Keefe 2001). The authors reviewed 24 studies – five of which reported on a single industry-funded clinical trial – and concluded that although *second-generation antipsychotics* (SGAs) 'appear to have preliminary promise for the enhancement of cognitive functioning (…), the methodology for assessing the treatment of cognitive deficits is still being developed (and thus) researchers and clinicians alike need to approach publications in this area with a watchful eye toward methodological weaknesses that limit the interpretability of findings.'

The first concrete effort aimed at promoting research on cognitive-enhancing drugs for people with schizophrenia began in March 2001. Steve Hyman, then Director of NIMH (1995-2001), asked Wayne Fenton and Ellen Stover also at NIMH to develop a 'program in treatment development [that] led to the selection of cognitive impairment as a particularly promising new target, and a request for proposals to address some of the important obstacles that should be addressed to facilitate drug development in this area' (Stover, Brady et al. 2007). Hyman's motives for this decision are not known but Robert Buchanan believes that Michael Green's 1996 paper and subsequent studies that argued for the relationship between cognitive impairments and poor functional outcome were an important influence (Buchanan: Personal Communication 2012). For his part, Michael Green believes that Wayne Fenton played a key role in advancing this initiative based on his assessment that although cognition was a determinant of outcome and disability for people with schizophrenia and hence, it had major public health implications, he was aware that the FDA would not approve drugs in this area without a clear consensus about methods and measurement (Green: Personal Communication 2011).

Two years later, in 2003, Steve Hyman and Wayne Fenton published a paper entitled 'Medicine. What are the right targets for psychopharmacology?', in which they posited that it may be unrealistic for a drug to be effective for all the 'component symptom complexes' of schizophrenia, thus recommending that drug development focus on components that may be more proximate to the pathophysiology (Hyman and Fenton 2003). This paper has been cited as a key contribution to the re-conceptualization of schizophrenia as a

syndrome with multiple domains of dysfunction rather than as a single illness with one diagnosis, one treatment, and an explanatory pathophysiology (Tamminga 2008). In a 2007 paper entitled 'New Paradigms for Treatment Development', Ellen Stover and colleagues concurred, asserting that Hyman and Fenton's paper helped to reorient treatment development (Stover, Brady et al. 2007). However, this is not a new concept. First articulated by Kraepelin (Kraepelin 1987), the concept was re-discovered by Carpenter, Bartko, and Strauss in 1974 (Bartko, Strauss et al. 1974). In addition, the paper by Hyman and Fenton was largely influenced by the work and a series of papers published by Carpenter and colleagues on primary negative symptoms of schizophrenia and the domains of psychopathology (Carpenter, Heinrichs et al. 1988; Buchanan and Carpenter 1994; Carpenter Jr, Arango et al. 1999; Kirkpatrick, Buchanan et al. 2001) (Buchanan: Personal Communication 2012). Agreement exists, however, on the critical role played by Fenton in transforming this conceptual shift into material support for pro-cognitive research in the US (Buchanan: Personal Communication 2012) (Green: Personal Communication 2011). In the words of Stover and colleagues, Wayne Fenton 'was the individual, who demonstrated extraordinary leadership within NIMH by translating these ideas into effective Institute initiatives' (Stover, Brady et al. 2007).

An important methodological paper was published by researchers affiliated with University of California San Diego (UCSD) in the spring of 2001 which reported on the development of the *UCSD Performance Based Skills Assessment* (UPSA), a 'measure of everyday functioning for severely mentally ill adults' (Patterson, Goldman et al. 2001). UPSA is a performance-based measure that assesses five aspects of functional capacity affected by cognitive deficits in this population: household chores, communication, finances, transportation and planning recreational activities. Developing this scale was important because it provided a tool to assess the effects of pro-cognitive drugs on meaningful functional outcomes.

The first published report of a study undertaken to assess the cognitive-enhancing effects of new compounds was published in October 2001, when US researchers reported that a pilot study had found that augmentation of clozapine with AMPAkine CX-516, an experimental glutamate-stimulating compound, improved memory and attention (Goff, Leahy et al. 2001). However, a larger study published seven years later that used this same compound to augment a larger group of antipsychotics (clozapine, olanzapine and risperidone) failed to replicate the initial finding (Goff, Lamberti et al. 2008). The authors stated that, given the similarity in study design, 'the difference in results most likely reflects a failure of a small sample to predict outcomes for larger trials.'

In 2003, the NIMH programme conceived by Steve Hyman, Wayne Fenton, and Ellen Stover came to fruition with the launching of the NIMH-funded contract to Stephen Marder and Michael Green, both at University of California Los Angeles (UCLA), known as *Measurement and Treatment Research to Improve Cognition in Schizophrenia* (MATRICS). The stated aims of the MATRICS initiative were 'to identify the most promising science-based ideas regarding the neurochemical basis of (cognitive) deficits, and to achieve a broad academic, industry, and regulatory agreement on the best way to measure cognition in clinical trials'. (http://www.nimh.nih.gov/science-news/2004/research-to-test-treatment-of-cognitive-dysfunction-in-schizophrenia.shtml). Although MATRICS's goal was to construct a pathway to drug approval, the lack of a

consensus battery to measure cognitive deficits made it necessary for MATRICS investigators to focus on the development of such a battery as their first endeavour (Green: Personal Communication 2011). Marder and Green assembled representatives from academia, government and industry to organise a series of six conferences on various aspects of treatment development for cognitive impairment in schizophrenia. According to Stover and colleagues, the ability of MATRICS investigators to 'organize important interactions with FDA (was) one of its important accomplishments' (Stover, Brady et al. 2007). At the first MATRICS consensus conference held in April 2003, the NIMH convened academic, industry and regulatory experts under the MATRICS initiative to review available data demonstrating the central role of cognition in schizophrenia. It was agreed then that it was necessary to develop a consensus battery specifically designed to assess cognitive performance in people affected with the illness, and that cognitive performance would be the primary outcome measure for pro-cognitive R&D efforts (Green 2006; Buchanan, Keefe et al. 2011)(Green: Personal Communication 2011). An examination of the domains that should be represented in the battery that began at the conference (Green: Personal Communication 2011) was furthered by a group of MATRICS researchers who set out to evaluate the existing empirical evidence. They concluded that:

> seven separable cognitive factors [...] represent fundamental dimensions of cognitive deficit in schizophrenia: Speed of Processing; Attention/Vigilance; Working Memory; Verbal Learning and Memory; Visual Learning and Memory; Reasoning and Problem Solving; and Verbal Comprehension. An eighth domain, Social Cognition, was added due to recent increased interest in this area and other evidence of its relevance for clinical trials aiming to evaluate the impact of potential cognitive enhancers on cognitive performance and functional outcome. Verbal Comprehension was not included in the cognitive battery due to its resistance to change.
>
> (Nuechterlein, Barch et al. 2004).

The battery was eventually named MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein and Green 2006). In April 2004, MATRICS investigators organised an FDA/NIMH consensus meeting with participation of representatives from academia and industry to develop guidelines for the design of clinical trials of cognitive-enhancing drugs for people with schizophrenia (FDA-NIMH-MATRICS guidelines). The workshop developed recommendations for subject selection, co-primary outcome measures, and statistical approaches for study design. According to Robert Buchanan and colleagues, the FDA's clarification that drug approval was contingent on concurrent change on a co-primary measure of functional outcome was among 'the most difficult issues' discussed at the conference because of feasibility concerns (Buchanan, Davis et al. 2005). Additionally, unlike the measure for cognitive performance, 'the FDA did not provide firm guidance on the definition of a functionally meaningful co-primary measure' (Green, Schooler et al. 2011). However, the FDA expressed willingness 'to accept a co-primary measure with good face validity, whether a proxy measure of community outcome or an interview-based measure of cognition, before formal validation of a co-primary measure is completed' (Buchanan, Davis et al. 2005).

Further NIMH support for research on cognition in schizophrenia was awarded in May 2004, a four-year contract to UCLA and five other academic medical centers to create a network of *Treatment Units for Research on Neurocognition and Schizophrenia* (TURNS) aimed at selecting and testing potential cognitive-enhancing drugs (PI: Stephen Marder). The programme developed a network of academic sites in order to evaluate potential efficacy of novel agents in proof-of-concept trials (Buchanan, Javitt et al. 2007). On announcing the award, NIMH stated that 'TURNS is one component of a multipronged NIMH effort to stimulate academic and industry sponsored research focused on cognitive deficits in schizophrenia.' Although no longer receiving federal support, some of the TURNS studies are still ongoing under the auspices of the *Treatment and Evaluation Network for Trials in Schizophrenia* (TENETS) network (Geyer 2010). To date, no clearly efficacious agent has been identified by TURNS-sponsored studies (Geyer 2010; Marder 2011).

The final MATRICS meeting ('New Approaches Conference') held in September 2004 aimed to develop an NIMH research agenda to address critical scientific issues identified through the MATRICS process. Two important initiatives were born at that meeting: (1) research conducted by a TURNS subgroup chaired by Mark Geyer, whose aim is to evaluate animal models for each of the cognitive domains from MATRICS, and (2) the decision by Deanna Barch and Cameron Carter to develop a research programme that would use the tasks and tools derived from cognitive neuroscience to more precisely measure cognition in schizophrenia drug discovery. Thus evolved the *Cognitive Neuroscience Treatment to Improve Cognition in Schizophrenia* (CNTRICS) initiative also sponsored by NIMH (Carter and Barch 2007; Stover, Brady et al. 2007; Geyer 2010). The first CNTRICS meeting was held in February 2007 (http://cntrics.ucdavis.edu/index.shtml). CNTRICS I held three meetings; its successor, CNTRICS II, held four meetings (October 2009 – April 2011).

Throughout this period, interest in the cognitive effects of antipsychotics had not faded away. In 2004, Aaron Mishara and Terri Goldberg published a meta-analysis of studies that compared cognitive effects of FGAs versus placebo or no medication among patients with schizophrenia, concluding that FGA treatment is associated with modest-to-moderate gains in multiple cognitive domains (Mishara and Goldberg 2004). Work by investigators affiliated with Sherbrooke University in Canada and presented at the 20th European College of Neuropsychopharmacology Congress in Vienna in 2007 (Elie, Poirier et al. 2010) examined the cognitive effects of antipsychotic polypharmacy and dosage. This study found that cognitive performance was inversely associated with dose, even at low doses and independent of the number of drugs used.

Although consensus existed that MATRICS had accomplished what it had set out to accomplish, discussions among US representatives from industry and academia held in February 2007 led to the identification of two remaining obstacles to drug development: (1) the lack of non-English versions of MCCB, problematic because 'most drug development was international,' and (2) 'the need for co-primary measures that could be used in large international trials' (Stover, Brady et al. 2007). This led to the development of MATRICS *Co-primary and Translation* (CT) (MATRICS CT), a programme of research led by Stephen Marder (academia) and Brendon Binneman (pharmaceutical

industry), which although sponsored by NIMH, was supported through donations of a partnership of pharmaceutical companies to the Foundation at NIMH.

The body of evidence on the cognitive effects of antipsychotics was expanded with the publication in June 2007 of a study by *Clinical Antipsychotic Trials of Intervention Effectiveness* (CATIE) investigators which assessed the neurocognitive effects of perphenazine, an FGA, and the SGAs risperidone, olanzapine, quetiapine and ziprasidone (Keefe, Bilder et al. 2007). They found that two months into the study, all groups had a small but significant improvement in neurocognition as measured by change in a composite score derived from eleven neurocognitive tests, yet exploratory analyses suggested that perphenazine may exhibit the 'most neurocognitive improvement.' The authors acknowledged that their results were at odds with 'numerous published studies and 3 meta-analyses suggesting neurocognitive advantages' of SGAs relative to FGAs. They also found that patients who required anticholinergic drugs did not exhibit the modest cognitive benefit associated with antipsychotic treatment. The authors acknowledged several limitations, including that at least 60% of study patient had received an SGA prior to randomisation.

Negative results of pro-cognitive pharmacological interventions came to light in 2007. In October that year, Robert Buchanan and colleagues published findings from the *Cognitive and Negative Symptoms in Schizophrenia Trial* (CONSIST), an RCT that assessed the effects of two glycinergic agents on negative symptoms and cognitive functions in patients with schizophrenia or schizoaffective disorder (Buchanan, Javitt et al. 2007). The authors found that neither of the agents used in the trial were 'generally effective therapeutic options for treating negative symptoms or cognitive impairments.' Also that year, Canadian researchers affiliated with the University of Montreal published the results of a study of randomised crossover design that assessed the cognitive effects of rivastigmine, a cholinergic agent used to treat mild to moderate dementia, as add-on to antipsychotics (Chouinard, Stip et al. 2007). The study, supported by an Investigator Initiative Trial proposed to Novartis Canada and by the University of Montreal Eli Lilly Canada Chair in Schizophrenia Research (held by Professor Emmanuel Stip), did not find significant improvement in any cognitive variables following rivastigmine treatment.

In January 2009, the European Commission approved funding to be funnelled through a combination of governmental and pharmaceutical industry funds for the improvement of preclinical–clinical translation via partnerships between industry and academia. This research programme, *Novel Methods leading to New Medications in Depression and Schizophrenia* (NewMeds), is part of the *Innovative Medicines Initiative* (IMI), a public–private partnership between the European Union and the European Federation of Pharmaceutical Industries and Associations (www.imi.europa.eu). NewMeds' well-funded programme on psychiatric drug discovery includes a substantial focus on drugs to treat the cognitive impairments associated with schizophrenia; among other goals, it will seek to address basic research issues that MATRICS did not quite resolve (Geyer 2010)(Kapur: Personal Communication, 2012). Described as a 'very unusual public–private collaboration', NewMeds is a five-year, €20 million (US$28 million) effort that includes seven academic partners, nine pharmaceutical companies and a few biotech companies (Abbott 2010). Mark Geyer, a UCSD-affiliated researcher involved in both NewMeds and CNTRICS, wrote in his 2010 paper entitled 'New Opportunities in the Treatment of

Cognitive Impairments Associated with Schizophrenia' that an encouraging and critically important aspect of this initiative is the openness of European governments to support, and the pharmaceutical companies to participate in, cooperative efforts involving multiple companies and multiple academic institutions (Geyer 2010). Because of the more complicated relationship between industry and regulators, funders and academics in the US (Kapur: Personal Communication, 2012), the paradigm of public–private collaboration represented by NewMeds is seen by some as a good model for the US to adopt. Again in the words of Geyer:

> Many believe that the scope of work required to develop useful preclinical screening tests for cognitive enhancers is such that coordinated collaborations among multiple pharmaceutical companies and many academic laboratories will be critically important. Although the development of a collaborative preclinical trials network for cognitive impairments in schizophrenia was suggested by the MATRICS group, it is difficult for industry to share data and work openly with academia. Some such collaborative efforts appear to have been initiated successfully by NewMeds. There is not yet a safe harbor in the United States for a similar organized effort to foster data sharing and for cooperation to flourish, even if it is limited to studies of established compounds that are no longer patented. Such an effort would be highly recommended and could have a significant impact.
>
> (Geyer 2010)

Further evidence on the cognitive effects of antipsychotics was published in June 2009, when a consortium of European and Israeli researchers (European Group for Research in Schizophrenia) reported on results from the *European First Episode Schizophrenia Trial* (EUFEST), an industry-funded randomised open-label clinical trial (N= 498) (Davidson, Galderisi et al. 2009). The authors concluded that 'treatment with antipsychotic medication is associated with moderate improvement in the cognitive test performance of patients who have schizophreniform disorder or who are in their first episode of schizophrenia', and that improvement did not differ across antipsychotics (haloperidol, an FGA, and the SGAs amisulpiride, olanzapine, quetiapine and ziprasidone). In addition, the authors found a weak association between cognitive improvement and symptom change. However, in an editorial accompanying the EUFEST paper, Terri Goldberg cautioned that practice effects and other factors need to be considered when evaluating the positive findings of both CATIE and EUFEST (Goldberg and Gomar 2009).

In January 2010, Robert Buchanan and other *Patient Outcomes Research Team* (PORT) researchers published the 2009 Schizophrenia PORT Psychopharmacological Treatment Recommendations, an influential US clinical guideline for the treatment of schizophrenia (Buchanan, Kreyenbuhl et al. 2010). PORT researchers took up treatments to improve cognition for the first time since the original recommendations were published in 1998. In this regard, they wrote:

> People with schizophrenia are characterized by a broad range of cognitive impairments. These impairments are a core component of the illness, are robustly associated with

> poor outcomes in schizophrenia, and represent a major unmet treatment need. A large number of studies have examined the efficacy of (first- and second-generation antipsychotic) medications for cognitive impairments, with little evidence that these agents have significant cognitive-enhancing effects. In addition, there is currently insufficient evidence to support the use of any adjunctive agent for the treatment of cognitive impairments in people with schizophrenia.

In 2010, a paper by MATRICS investigators and Thomas Laughren (Director of the FDA's Psychiatry Products Division) reported on the effects of the FDA-NIMH-MATRICS guidelines on the design of pro-cognitive drug trials (Buchanan, Keefe et al. 2011). The authors reported that several studies have examined the effect of pharmacological interventions on cognitive performance, many of which have used the FDA-NIMH-MATRICS guidelines as well as MCCB, and that by February 2010, 'several large-scale studies using the MCCB are currently underway' (http://clinicaltrials.gov/). Among the completed studies, two were TURNS trials and two were industry-sponsored (one of them a proof-of-concept trial cosponsored by Memory Pharmaceuticals Inc and F. Hoffmann-La Roche, Ltd, and another sponsored by Sunovion). Notably, however, several pharmaceutical companies announced that same year that they would stop conducting drug discovery research in schizophrenia. A *Nature* piece entitled 'Schizophrenia: The drug deadlock' published in November 2010 stated that 'under intensifying pressure to rein in costs, several large companies, including London-headquartered AstraZeneca and GlaxoSmithKline, chose to pull out of psychiatric pharmacology altogether' (Abbott 2010). Judith Jaeger PhD, with AstraZeneca, emphasised that the company's decision only affects their drug discovery operation, as they hope to continue to develop psychiatric drugs discovered by biotechs or other partners (Jaeger: Personal Communication (2011).

Research on the pro-cognitive effects of novel compounds has continued, however. In March 2011, Robert Buchanan and colleagues published the results of a TURNS-sponsored RCT that examined the efficacy and safety of a GABA partial agonist (MK-0777) relative to placebo for the treatment of cognitive impairments in stable patients with schizophrenia (Buchanan, Keefe et al. 2011). The primary outcome was cognitive improvement assessed through the MCCB, and functional capacity was the co-primary outcome. Contrary to pilot evidence suggesting that the molecule had positive effects on delayed memory and cognitive measures of prefrontal cortical function, the authors did not find group differences on any of the study measures.

Research on the effects of antipsychotics on brain anatomy and function was furthered by the publication in February 2011 of results of a longitudinal study of treated patients with schizophrenia followed with serial MRI (Ho, Andreasen et al. 2011). The authors found that the amount of exposure to antipsychotic medication predicted decrements in cerebral gray and white matter volumes and increased the volume of the putamen. They also found that changes in brain volume with time persisted after accounting for illness duration and severity effects, and that they were similar for all classes of antipsychotic medications, including clozapine. In an accompanying editorial, David Lewis wondered if the observed reductions in brain volume 'impair function or are they related to the therapeutic benefits of these medications?', adding that 'the idea that strategic reductions in brain volume can

be functionally beneficial is supported by the improvements in cognitive capacity that accompany cortical gray matter volume reductions during adolescence' (Lewis 2011). He could not discount, however, that as suggested by Ho and colleagues, antipsychotics may 'improve symptoms and contribute to progressive brain tissue reductions through different actions on separate brain circuits.'

MATRICS investigators have continued to work on the important line of research focused on co-primary measures. In April 2011, they published the results of the MATRICS-CT-sponsored *Validation of Intermediate Measures* (VIM) study, whose aim was to validate co-primary measures, including those identified in the *Psychometric and Standardization Study* (PASS), a previous MATRICS study (Green, Schooler et al. 2011). The authors assessed UPSA and other performance-based tests of functional capacity, as well as an interview-based assessment of cognition. Their findings led the VIM Committee to consider UPSA as the leading co-primary measure.

Research on cognitive remediation therapy for schizophrenia has yielded very important insights for the field. In May 2011, Til Wykes and colleagues published a meta-analysis of this research published up to June 2009 (Wykes, Huddy et al. 2011). The authors found that the intervention 'yielded durable effects on global cognition and functioning'. While they found that no treatment element (remediation approach, duration, computer use, etc) was associated with cognitive outcome, the authors found 'significantly stronger effects on functioning (…) when cognitive remediation therapy was provided together with other psychiatric rehabilitation.' Their results were not moderated by methodological rigor. The authors concluded that 'cognitive remediation benefits people with schizophrenia, and when combined with psychiatric rehabilitation, this benefit generalizes to functioning, relative to rehabilitation alone.'

Although more studies on the cognitive effects of antipsychotics may be forthcoming, the verdict seems to be in. In 2011, Terri Goldberg and colleagues asserted that the conclusion that SGAs 'have not been shown to enhance cognition is in keeping with the emerging evidence that (in contrast to earlier views), they do not have a distinct advantage in antipsychotic efficacy, or a unifying or distinctive pharmacology (compared to FGAs)' (Goldberg, Keefe et al. 2010). They added that this conclusion 'is also consistent with the fact that D_2 receptor blockade, the property shared by all antipsychotics, is not clearly beneficial for cognitive processes in healthy human subjects or in animals, and may be impairing.'

7.7 Observations

Factors that may have acted as **barriers** to the recognition of the importance of cognitive deficits as a target for pharmacological treatment in schizophrenia, the development of valid/reliable means to measure these deficits, the development of cognitive-enhancing drugs, or a clearer/prompter understanding of the cognitive effects of antipsychotic drugs include:

- The unitary model of schizophrenia (single disease entity with one diagnosis, one treatment, and one explanatory pathophysiology), which discouraged the development of treatments targeted to specific domains of psychopathology.

- Although a robust body of scientific neuropsychological evidence exists on the neural circuits, neurotransmitters, and brain regions implicated in the cognitive deficits of schizophrenia, pro-cognitive drug R&D may be hampered by:

    - limited knowledge in some areas of basic research (eg animal models of cognition, pre-clinical to clinical translation) (Kapur: Personal Communication, 2012)

    - the complexity inherent to measuring cognitive deficits in patients with schizophrenia and how valid the assumptions are (ie how much of the measures are confounded by secondary phenomena, such as drug treatment, motivation, environmental deprivation, and general psychological factors, and also how general the deficit might be) (Weinberger: Personal Communication 2011)

    - the possibility that psychosocial interventions such as training exercises may be necessary for pro-cognitive drugs to manifest their latent effectiveness (Green: Personal Communication 2011) (Kapur: Personal Communication, 2012).

- The development of pro-cognitive drugs for people with schizophrenia requires effective partnerships between academic researchers and the pharmaceutical industry, an ideal that may be complicated by:

    - the complicated relationship between industry representatives and regulators, funders and academics in the US (Kapur: Personal Communication, 2012) (Buchanan: Personal Communication 2012)

    - the pharmaceutical industry's decision to pull out of psychiatric drug discovery (Green: Personal Communication 2011) (Jaeger: Personal Communication (2011) (Buchanan: Personal Communication 2012).

- The decision by the FDA to require a co-primary measure, which may have dampened the enthusiasm of industry to engage in R&D because of the methodological challenges associated with assessing functioning in short-term trials (Kapur: Personal Communication, 2012) (Buchanan: Personal Communication 2012) (Green: Personal Communication 2011), or the ability of the measure to validly assess change across the globe (Jaeger: Personal Communication (2011).

Some of the factors that may have **facilitated** the recognition of the importance of cognitive deficits as a target for pharmacological treatment in schizophrenia, the development of valid/reliable means to measure these deficits, the development of cognitive-enhancing drugs, or a clearer/prompter understanding of the cognitive effects of antipsychotic drugs include:

- Basic research by Weinberger and colleagues (showing that cognitive function could be predicted through measures of brain structure and function), and by Goldman-Rakic and colleagues (on neural circuits and neurotransmitters that support working memory),

which made cognition in schizophrenia a scientifically interesting and tractable question (Kapur: Personal Communication, 2012).

- Research demonstrating that cognitive function – and not necessarily psychiatric symptomatology – is the best predictor of functional outcomes (Kapur: Personal Communication, 2012).

- In the US, the FDA's willingness to approve drugs whose sole indication is improvement of cognitive function in schizophrenia, which may have prodded European regulators to move in the same direction (Green: Personal Communication 2011). This stance by the FDA may have been facilitated by:

    - the high-profile debunking of the unitary model of schizophrenia, and the re-conceptualisation of schizophrenia as a syndrome with multiple domains of dysfunction.

    - its 2002 decision to approve a second indication for clozapine (suicidality), which in effect opened the door for obtaining indications for other domains of psychopathology (Meltzer: Personal Communication 2012).

- In the US, Wayne Fenton's advocacy, and funding and logistical support from NIMH (Buchanan: Personal Communication 2012).

- Multi-disciplinary research collaborations between basic researchers and psychiatrists, some of whom worked together on research related to negative symptoms of schizophrenia (Buchanan: Personal Communication 2012).

- Realisation that available antipsychotic drugs have minimal cognitive benefits (Green: Personal Communication 2011).

- The pharmaceutical industry's persistent interest in R&D in neuroscience, and their interest in partnering with a smaller bio-tech company that would conduct psychiatric drug discovery (ie, the initial animal studies and phase I trials) (Jaeger: Personal Communication 2011).

1909

1909 Emil Kraepelin suggests several psychotic conditions are part of a single disease entity (he termed this dementia praecox)

1937 Altman and Shakow publish the first of a series of studies on intelligence, thinking, and memory (conducted at Worcester State Hospital from 1927-1946 Study shows people with schizophrenia performed worse on a test of "thinking disturbance."

1939 Cameron publishes a paper in which he posits that over-inclusive thinking is at the core of disordered thinking in schizophrenia (Cameron 1939).

1958

1958 Whitehead and Tune (1958) assess chlorpromazine's effects on the learning process and on verbalized social adaptation in a group of hospitalized chronic psychotic patients. Conclude there is no significant effect on the learning process but an effect on motivation.

1960

1961 Vestre (1961) reports on a placebo-controlled study using a word association task to assess the effect of chlorpromazine on learning; study concludes chlorpromazine affected "learning and retention negatively."

1964 Weaver and Brooks (1964) report on a study that assesses if performance on neurocognitive tests predicts acquisition of psychosocial skills needed for community functioning. The study finds patients with schizophrenia exhibited significant slowness on a variety of psychomotor tests.

1968 Results from the first RCT on cognitive remediation in schizophrenia conducted among inpatients with schizophrenia are published. Study concludes noncomputerized attention training led to substantial improvements in visual learning memory and reasoning & problem solving (Wagner, in (McGurk, Twamley et al. 2007)).

1970

1975

1976 Johnstone, Crow et al (1976) publish a study showing increased cerebral ventricular size among 17 institutionalized patients with schizophrenia relative to age-matched employed controls.

1978 Heaton, Vogt et al (1979) publish a paper comparing schizophrenic patients and 25 normal controls, which finds that neuropsychological impairment had a higher correlation with degree of EEG abnormality than with degree of psychosis. This suggests a possible organic basis for the deficits exhibited by patients.

1980

1982 (April) Feinberg (1982) publish a paper in which they posit abnormal rates of programmed cell elimination during adolescence contributes to cognitive impairment and psychotic symptoms with schizophrenia (Lesh, Niendam et al. 2011).

1984 A comparative study is published, reporting on verbal recall and recognition among normal controls and patients with schizophrenia on antipsychotic drugs alone or co-prescribed with anticholinergic medications (Calev 1984). Finds patients with schizophrenia taking both classes of drugs had the worst performance on cognitive tests.

1986 (February) The first of several studies simultaneously evaluated dorsolateral prefrontal cortex (DLPFC) physiology and function among patients with schizophrenia is published. Provides evidence on physiologic dysfunction (Weinberger, Berman et al. 1986).

1987

1987 (July) A study is published That suggests the development of symptoms of schizophrenia is the end result of an early developmental pathology, particularly in the DLPFC, affecting normal brain maturational events occurring much later (Weinberger 1987).

1987 (November) A study is released that investigates the potential reversibility of cognitive deficits and the role of state variables such as attention and motivation among patients with schizophrenia (Goldberg, Weinberger et al. 1987).

1987 Stephen Stahl, then-affiliated with Merck Sharp & Dome Research Laboratories, publishes a paper that wishes for psychopharmacological innovations are agents to enhance cognitive failure for schizophrenia (Stahl 1987).

1989 A research review is published on the influence of antipsychotic and anticholinergic drugs on cognitive processes in schizophrenia (Spohn and Strauss 1989). This concludes that the use of antipsychotic drugs is associated with limited normalization on many psychological measures, whereas anticholinergics appear to disrupt some aspects of memory.

1990

1990 (March) A literature review is published on the effects of first generation antipsychotics on perceptual and neuropsychological function in patients with chronic schizophrenia (Cassens, Inglis et al. 1990).

1990 (November) Report of a study is published, assessing assessed pairs of monozygotic twins discordant for schizophrenia on a range of neuropsychological tests (Goldberg, Ragland et al. 1990). Finds affected twins tended to perform worse than their unaffected counterparts on most of the tests.

1991 Study published in Science indicating D1 dopamine receptors located in the prefrontal cortex are involved in working memory (Sawaguchi and Goldman-Rakic 1991).

1992 (May) Meltzer (1992) publishes a study on the effects of clozapine among treatment-resistant patients with schizophrenia. Reports significant improvement in several domains, including some types of cognitive function.

1994

1993 (January) Goldberg, Greenberg et al. (1993) report a study on the cognitive effects of clozapine that finds cognitive functions were essentially unchanged, and that cognitive disability was rate-limiting in the sample's functional rehabilitation.

1993 (November) Hagger, Buckley et al. (1993) publishes a study assessing cognitive functions and psychopathology in treatment-refractory patients with schizophrenia before initiation of clozapine, and at follow-up. At follow-up, researchers found improvement in measures of retrieval from reference memory and in some tests of executive function, attention, and recall memory.

1994 (February) Saykin, Shtasel et al. (1994) published, which concluded that verbal memory is a primary neuropsychological deficit present early in the course of schizophrenia.

1994 (November) Goldman-Rakic (1994) publish a paper concluding there is a robust body of evidence To support the theory that a defect in working memory "may be the fundamental impairment leading to schizophrenic thought disorder" (Goldman-Rakic 1994).

1994 (December) The first controlled study is published, which assesses the cognitive effects of clozapine (Buchanan, Holstein et al. 1994). Authors found short- and long-term advantages for clozapine.

1997

1995 (September) Goldberg, Torrey et al (1995) publish a study that Looks at three sets of monozygotic twin pairs to study cognitive measures of genetic risk in schizophrenia. They find large differences between unaffected and affected members of discordant pairs on a wide variety of cognitive variables.

1995 (December) A synthesis paper is published on neurobiological and cognitive science literature on the role of the prefrontal cortex in executive functions (Goldman-Rakic 1995).

1996 A review paper Is published on "which, if any, neurocognitive deficits restrict the functioning of patients with schizophrenia in the outside world" (Green 1996). Concludes that various cognitive deficits were predictive of functional outcomes whereas (positive) psychotic symptoms were not.

1997 Goldman-Rakic and Selemon (1997) publish on "recount efforts to dissect the cellular and circuit basis of working memory with the goal of extending the insights gained from the study of normal brain organization in animal models to an understanding" of schizophrenia.

1998 A meta-analysis Is published on neurocognitive literature on test performance in schizophrenia (Heinrichs and Zakzanis 1998). Results indicate "schizophrenia is characterized by a broadly based cognitive impairment with varying degrees of deficit in all ability domains measured by standard clinical tests."

2001

2001 (February) The American Journal of Psychiatry publishes a review of studies on drug-mediated cognitive enhancement (Harvey and Keefe 2001). The authors conclude that although second generation antipsychotics (SGAs) "appear to have preliminary promise for the enhancement of cognitive functioning (…), the methodology for assessing the treatment of cognitive deficits is still being developed".

2001 (March) The Director of NIMH's plans to develop a programme in treatment development leads to selection of cognitive impairment as a new target and a request for proposals to address some of the important obstacles in drug development in this area.

2001 (Spring) Schizophrenia Bulletin reports on a "new measure of everyday functioning for severely mentally ill adults" named UCSD Performance Based Skills Assessment (UPSA)" (Patterson, Goldman et al. 2001).

2001 (October) A pilot study is published on clozapine with an experimental glutamate-stimulating compound resulted in improvement in memory and attention (Goff, Leahy et al. 2001). However, a larger study adding the same compound to clozapine, olanzapine, and risperidone fails to replicate this earlier finding.

2002 Hyman and Fenton (2003) publish a paper in Science that makes a key contribution to the re-conceptualization of schizophrenia as a syndrome with multiple domains of dysfunction rather than as a single illness with one diagnosis, one treatment, and an explanatory pathophysiology.

2003 The NIMH-funded contract to UCLA launches the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative. This aims to identify promising science-based ideas on the "neurochemical basis of (cognitive) deficits, and to achieve a broad academic, industry, and regulatory agreement on the best way to measure cognition in clinical trials"

2003 (April) The first MATRICS consensus conference is convened by NIMH. It involves academics, industry and regulatory experts. The battery is eventually named MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein, Barch et al. 2004)

2004

2004 (May) NIMH awards a 4-year contract to UCLA and five other academic medical centers to create a network of Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) aimed at selecting and testing potential cognitive-enhancing agents (PI: Stephen Marder).

2004 (April) MATRICS investigators organise another consensus meeting sponsored by the US Food and Drug Administration (FDA) and NIMH to develop recommendations for subject selection, co-primary outcome measures, and statistical approaches for study design. At the meeting, the FDA clarified that "approval of a neurocognitive drug for schizophrenia" was contingent on "concurrent change on a co-primary measure of functional outcome

2004 (September) The final MATRICS meeting ("New Approaches Conference") Is held; this aims to develop a research agenda to address scientific issues identified through the MATRICS process, and leads to the Cognitive Neuroscience Treatment to Improve Cognition in Schizophrenia (CNTRICS) initiative (Carter and Barch 2007; Stover, Brady et al. 2007; Geyer 2010).

2004 A meta-analysis of studies that compared cognitive effects of first generation antipsychotics versus placebo or no medication among patients with schizophrenia is published. Authors find modest-to-moderate gains in multiple cognitive domains (Mishara and Goldberg 2004).

2007 (February). The first of three meetings Is held of the completed first round of CNTRICS. CNTRICS II is also completed, held 4 meetings (October 2009 – April 2011).

2007 (February) MATRICS CT (Coprimary selection and Translation of the MCCB) is formed, in response to obstacles in drug development. This is an NIMH program led by Stephen Marder and Brendon Binneman and supported through donations of a partnership of pharmaceutical companies to the Foundation at NIMH.

2007 (June) A study is published on the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) whose aim was to compare the neurocognitive effects of Phase I antipsychotics (Keefe, Bilder et al. 2007). Finds 2 months into the study that all groups had a small but significant improvement in neurocognition.

2007 (October) A paper reports on the results of a study that assessed the effects of glycinergic agents on negative symptoms and cognitive functions in patients with schizophrenia (Buchanan, Javitt et al. 2007). Finds neither of the agents used were "generally effective therapeutic options for treating negative symptoms or cognitive impairments

2009

2009 (January) The European Commission approves funding for preclinical-clinical translation research under the program Novel Methods Leading to New Medications in Depression and Schizophrenia (NewMeds), part of the Innovative Medicines Initiative. Funds set aside for a program on psychiatric drug discovery, including drugs to treat the cognitive impairments associated with schizophrenia (Geyer 2010)

2009 (June) Results from the European First Episode Schizophrenia Trial (EUFEST), an industry-funded open-label RCT (N= 498) are published (Davidson, Galderisi et al. 2009). The authors concluded that "treatment with antipsychotic medication is associated with moderate improvement in the cognitive test performance."

2009 (June) In an editorial accompanying the EUFEST study, Terry Goldberg states that practice effects and other factors need to be considered when evaluating the positive findings of both CATIE and EUFEST (Goldberg and Gomar 2009).

2010

2010 (January) 2009 Schizophrenia Patient Outcomes Research Team (PORT) psychopharmacological treatment recommendations and summary statements Are published (Buchanan, Kreyenbuhl et al. 2010). Concludes there is little evidence that first and second generation antipsychotics have significant cognitive enhancing effects, and insufficient evidence to support using adjunctive agents in the treatment of cognitive impairments in people with schizophrenia.

2010 Several pharmaceutical companies including AstraZeneca, GlaxoSmithKline, and Sanofi announce that they will stop conducting schizophrenia research in a drive to focus R&D efforts and cut costs

2010 Paper published with a review by MATRICS investigators and the Director of the FDA's Psychiatry Products Division on the effect of pharmacological interventions on cognitive performance (Buchanan, Kreyenbuhl et al. 2010). Reports many of The studies used the FDA-NIMH-MATRICS guidelines as well as MCCB.

2011

2011 (February) Results of a longitudinal study of treated patients with schizophrenia followed with serial MRI are published (Ho, Andreasen et al. 2011). Finds the amount of exposure to antipsychotic medication predicted decrements in cerebral gray and white matter volumes and increased the volume of the putamen.

2011 (February) In an editorial commenting on the findings by Ho and colleagues, David Lewis wondered if reductions in brain volume associated with antipsychotic medications impair function or they are related to the therapeutic benefits of these medications (Lewis 2011). However, he cannot discount antipsychotics may improve symptoms and contribute to progressive brain tissue reductions

2011 (March) Results of a TURNS-sponsored RCT Are published on outcomes of a GABA partial agonist for the treatment of cognitive impairments in patients with schizophrenia (Buchanan, Keefe et al. 2011). The authors did not find group differences on the main outcome measure (MCCB) or the co-primary functional measures.

2011 (April) A paper by MATRICS investigators reports on the MATRICS-CT-sponsored Validation of Intermediate Measures (VIM) study, which aimed to validate co-primary measures (Green, Schooler et al. 2011). Their findings led the VIM Committee to consider UPSA as the leading co-primary measure.

2011 (May) A meta-analysis of studies of cognitive remediation therapy for schizophrenia published up to June 2009 is published (Wykes, Huddy et al. 2011). Concludes "cognitive remediation benefits people with schizophrenia, and when combined with psychiatric rehabilitation, this benefit generalizes to functioning, relative to rehabilitation alone."

7.8 References

Abbott, A. (2010). 'Schizophrenia: the drug deadlock.' *Nature* 468(7321), 158–159.

Altman and Shakow (1937). 'A comparison of the performance of matched groups of schizophrenic patients, normal subjects, and delinquent subjects on some aspects of the Stanford-Binet.' *Journal of Educational Psychology* 88, 519–529.

Bartko, J. J., Strauss, J. S. et al., (1974). 'Part II. Expanded Perspectives for Describing and Comparing Schizophrenic Patients.' *Schizophrenia Bulletin* 1(11), 50–60.

Buchanan, R. W. and Carpenter, W. T. (1994). 'Domains of psychopathology: an approach to the reduction of heterogeneity in schizophrenia.' *The Journal of Nervous and Mental Disease* 182(4), 193–204.

Buchanan, R. W., Davis, M., et al., (2005). 'A summary of the FDA-NIMH-MATRICS workshop on clinical trial design for neurocognitive drugs for schizophrenia.' *Schizophrenia Bulletin* 31(1), 5–19.

Buchanan, R. W., Holstein, C., et al., (1994). 'The comparative efficacy and long-term effect of clozapine treatment on neuropsychological test performance.' *Biological Psychiatry* 36(11), 717–725.

Buchanan, R. W., Javitt, D. C., et al., (2007). 'The Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST): the efficacy of glutamatergic agents for negative symptoms and cognitive impairments.' *American Journal of Psychiatry* 164(10), 1593–1602.

Buchanan, R. W., Keefe, R. S., et al., (2011). 'A randomized clinical trial of MK-0777 for the treatment of cognitive impairments in people with schizophrenia.' *Biological Psychiatry* 69(5), 442–449.

Buchanan, R. W., Keefe, R. S., et al., (2011). 'The FDA-NIMH-MATRICS guidelines for clinical trial design of cognitive-enhancing drugs: what do we know 5 years later?' *Schizophrenia Bulletin* 37(6), 1209–1217.

Buchanan, R. W., Kreyenbuhl, J., et al., (2010). 'The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements.' *Schizophrenia Bulletin* 36(1), 71–93.

Buchanan: Personal Communication (2012).

Calev, A. (1984). 'Recall and recognition in mildly disturbed schizophrenics: the use of matched tasks.' *Psychological Medicine* 14(2), 425–429.

Cameron, N. (1939). 'Deterioration and regression in schizophrenic thinking.' *Abnormal and Social Psychology* 34, 265–270.

Carpenter Jr, W. T., Arango, C., et al., (1999). 'Deficit psychopathology and a paradigm shift in schizophrenia research.' *Biological Psychiatry* 46(3), 352–360.

Carpenter, W. T., Heinrichs, D. W., et al. (1988). 'Deficit and nondeficit forms of schizophrenia: the concept.' *The American Journal of Psychiatry* 145(5), 578–583.

Carter, C. S. and Barch, D. M. (2007). 'Cognitive neuroscience-based approaches to measuring and improving treatment effects on cognition in schizophrenia: the CNTRICS initiative.' *Schizophrenia Bulletin* 33(5), 1131–1137.

Cassens, G., Inglis, A. K., et al., (1990). 'Neuroleptics: effects on neuropsychological function in chronic schizophrenic patients.' Schizophrenia Bulletin 16(3), 477–499.

Chouinard, S., Stip, E., et al., (2007). 'Rivastigmine treatment as an add-on to antipsychotics in patients with schizophrenia and cognitive deficits.' *Current Medical Research and Opinion* 23(3), 575–583.

Davidson, M., Galderisi, S., et al., (2009). 'Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: a randomized, open-label clinical trial (EUFEST).' *American Journal of Psychiatry* 166(6), 675–682.

Elie, D., Poirier, M., et al., (2010). 'Cognitive effects of antipsychotic dosage and polypharmacy: a study with the BACS in patients with schizophrenia and schizoaffective disorder.' *Journal of Psychopharmacology* 24(7), 1037–1044.

Feinberg, I. (1982). 'Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence?' *Journal of Psychiatric Research* 17(4), 319–334.

Geyer, M. A. (2010). 'New Opportunities in the Treatment of Cognitive Impairments Associated With Schizophrenia.' *Current Directions in Psychological Science* 19(4), 264–269.

Goff, D. C., Lamberti, J. S., et al., (2008). 'A placebo-controlled add-on trial of the Ampakine, CX516, for cognitive deficits in schizophrenia.' *Neuropsychopharmacology* 33(3), 465–472.

Goff, D. C., Leahy, L., et al., (2001). 'A placebo-controlled pilot study of the ampakine CX516 added to clozapine in schizophrenia.' *Journal of Clinical Psychopharmacology* 21(5), 484–487.

Goldberg, T. E. and Gomar, J. J. (2009). 'Targeting cognition in schizophrenia research: from etiology to treatment.' *American Journal of Psychiatry* 166(6), 631–634.

Goldberg, T. E., Greenberg, R. D., et al., (1993). 'The effect of clozapine on cognition and psychiatric symptoms in patients with schizophrenia.' *British Journal of Psychiatry* 162, 43–48.

Goldberg, T. E., Keefe, R. S., et al., (2010). 'Circumstances under which practice does not make perfect: a review of the practice effect literature in schizophrenia and its relevance to clinical treatment studies.' *Neuropsychopharmacology* 35(5), 1053–1062.

Goldberg, T. E., Ragland, J. D., et al., (1990). 'Neuropsychological Assessment of Monozygotic Twins Discordant for Schizophrenia.' *Archives of General Psychiatry* 47(11), 1066–1072.

Goldberg, T. E., Torrey, E. F., et al., (1995). 'Genetic risk of neuropsychological impairment in schizophrenia: a study of monozygotic twins discordant and concordant for the disorder.' Schizophrenia Research 17(1), 77–84.

Goldman-Rakic, P. S. (1994). 'Working memory dysfunction in schizophrenia.' Journal of Neuropsychiatry and Clinical Neurosciences 6(4), 348–357.

Goldman-Rakic, P. S. (1995). 'Cellular basis of working memory.' *Neuron* 14(3), 477–485.

Goldman-Rakic, P. S., Muly, E. C., et al., (2000). 'D(1) receptors in prefrontal cells and circuits.' *Brain Research Reviews* 31(2-3), 295–301.

Goldman-Rakic, P. S. and Selemon, L. D., (1997). 'Functional and Anatomical Aspects of Prefrontal Pathology in Schizophrenia.' *Schizophrenia Bulletin* 23(3), 437–458.

Green, M. F. (1996). 'What are the functional consequences of neurocognitive deficits in schizophrenia?' *American Journal of Psychiatry* 153(3), 321–330.

Green, M. F. (2006). 'Cognitive impairment and functional outcome in schizophrenia and bipolar disorder.' *Journal of Clinical Psychiatry* 67(10), e12.

Green, M. F., Schooler, N. R., et al., (2011). 'Evaluation of functionally meaningful measures for clinical trials of cognition enhancement in schizophrenia.' *American Journal of Psychiatry* 168(4), 400–407.

Green, M. F. : Personal Communication (2011).

Hagger, C., Buckley, P., et al., (1993). 'Improvement in cognitive functions and psychiatric symptoms in treatment-refractory schizophrenic patients receiving clozapine.' *Biological Psychiatry* 34(10), 702–712.

Harvey, P. D. and Keefe, R. S. (2001). 'Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment.' *American Journal of Psychiatry* 158(2), 176–184.

Heaton, R. K., Vogt, A. T., et al., (1979). 'Neuropsychological impairment with schizophrenia vs. acute and chronic cerebral lesions.' Journal of Clinical Psychology 35(1), 46–53.

Heinrichs, R. W. and Zakzanis, K. K. (1998). 'Neurocognitive deficit in schizophrenia: a quantitative review of the evidence.' *Neuropsychology* 12(3), 426–445.

Ho, B. C., Andreasen, N. C., et al., (2011). 'Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia.' *Archives of General Psychiatry* 68(2), 128–137.

Hyman, S. E. and Fenton, W. S. (2003). 'What Are the Right Targets for Psychopharmacology?' *Science* 299(5605), 350–351.

Jaeger, J. : Personal Communication (2012).

Johnstone, E. C., Crow, T. J., et al., (1976). 'Cerebral ventricular size and cognitive impairment in chronic schizophrenia.' *Lancet* 2(7992), 924–926.

Keefe, R. S., Bilder, R. M., et al., (2007). 'Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial.' *Archives of General Psychiatry* 64(6), 633–647.

Kirkpatrick, B., Buchanan, R. W., et al., (2001). 'A Separate Disease Within the Syndrome of Schizophrenia.' *Archives of General Psychiatry* 58(2), 165–171.

Kraepelin, E. (1987). *The clinical roots of the schizophrenia concept: translations of seminal European contributions on schizophrenia*. New York, NY, US: Cambridge University Press.

Lesh, T. A., Niendam, T. A., et al., (2011). 'Cognitive control deficits in schizophrenia: mechanisms and meaning.' *Neuropsychopharmacology* 36(1), 316–338.

Lewis, D. A. (2011). 'Antipsychotic medications and brain volume: do we have cause for concern?' *Archives of General Psychiatry* 68(2), 126–127.

Marder, S. R. (2011). 'Lessons from MATRICS.' *Schizophrenia Bulletin* 37(2), 233–234.

Marder, S. R. and Fenton, W. (2004). 'Measurement and Treatment Research to Improve Cognition in Schizophrenia: NIMH MATRICS initiative to support the development of agents for improving cognition in schizophrenia.' *Schizophrenia Research* 72(1), 5–9.

McGurk, S. R., Twamley, E. W., et al., (2007). 'A meta-analysis of cognitive remediation in schizophrenia.' *American Journal of Psychiatry* 164(12), 1791–1802.

Meltzer, H. Y. (1992). 'Dimensions of outcome with clozapine.' *British Journal of Psychiatry Suppl.* (17), 46–53.

Meltzer: Personal Communication (2012).

Mishara, A. L. and Goldberg, T. E. (2004). 'A meta-analysis and critical review of the effects of conventional neuroleptic treatment on cognition in schizophrenia: opening a closed book.' *Biological Psychiatry* 55(10), 1013–1022.

Nuechterlein, K. H., Barch, D. M., et al., (2004). 'Identification of separable cognitive factors in schizophrenia.' *Schizophrenia Research* 72(1), 29–39.

Nuechterlein, K. H. and Green, M. F. (2006). *MATRICS Consensus Cognitive Battery*. Los Angeles: MATRICS Assessment, Inc.

Patterson, T. L., Goldman, S., et al., (2001). 'UCSD Performance-Based Skills Assessment: development of a new measure of everyday functioning for severely mentally ill adults.' Schizophrenia Bulletin 27(2), 235–245.

Sawaguchi, T. and Goldman-Rakic, P. S. (1991). 'D1 dopamine receptors in prefrontal cortex: involvement in working memory.' *Science* 251(4996), 947–950.

Saykin, A. J., Shtasel, D. L., et al., (1994). 'Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia.' *Archives of General Psychiatry* 51(2), 124–131.

Spohn, H. E. and Strauss, M. E. (1989). 'Relation of neuroleptic and anticholinergic medication to cognitive functions in schizophrenia.' *Journal of Abnormal Psychology* 98(4), 367–380.

Stahl, S. M. (1987). 'Needs and opportunities for innovation in psychopharmacology.' *Journal of the Royal Society of Medicine* 80(7), 413–417.

Stover, E. L., Brady, L., et al., (2007). 'New paradigms for treatment development.' *Schizophrenia Bulletin* 33(5), 1093–1099.

Tamminga, C. A. (2008). 'Accelerating new knowledge in schizophrenia.' *American Journal of Psychiatry* 165(8), 949–951.

Vestre, N. D. (1961). 'The effects of thorazine on learning and retention in schizophrenic patients.' *Journal of Abnormal and Social Psychology* 63, 432–435.

Weaver, L. A., and Brooks, G. W. (1964). 'The Use of Psychomotor Tests in Predicting the Potential of Chronic Schizophrenics.' *Journal of Neuropsychiatry* 5, 170–180.

Weinberger, D. R. (1987). 'Implications of normal brain development for the pathogenesis of schizophrenia.' *Archives of General Psychiatry* 44(7), 660–669.

Weinberger, D. R., Berman, K. F., et al., (1986). 'Physiologic Dysfunction of Dorsolateral Prefrontal Cortex in Schizophrenia: I. Regional Cerebral Blood Flow Evidence.' *Archives of General Psychiatry* 43(2), 114–124.

Weinberger: Personal Communication (2011).

Whitehead, W. A. and Thune, L. E. (1958). 'The effects of chlorpromazine on learning in chronic psychotics.' *Journal of Consulting Psychology* 22(5), 379–383.

Wykes, T., Huddy, V., et al., (2011). 'A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes.' *American Journal of Psychiatry* 168(5), 472–485.