Australian Government
National Mental Health Commission

NATIONAL MENTAL HEALTH RESEARCH STRATEGY

BACKGROUND PAPER: Psychosis/psychotic disorders (Session 4C)

Professor Alison R Yung
NHMRC Professorial Fellow, Early Psychosis
The University of Melbourne

Introduction

Psychotic disorders such as schizophrenia can cause considerable disability and distress for the person and for their family or carers. They are costly from a personal, societal and economic perspective. Schizophrenia is the fifth leading worldwide cause of global disease burden among males and sixth among females.[1] In 2010 the estimated costs of psychotic disorders in Australia were $4.9 billion per year.[2]

Background

There is broad consensus on the following points:

- The course of psychotic disorders is variable. About 6% of individuals will experience a single episode, about 55% will have multiple episodes with good or partial recovery between the episodes; about 39% will have a continuous course.[3]
- There is a genetic component in psychotic disorders involving many genes of small effect as well as rare mutations in which the number of copies of specific regions of DNA are deleted or duplicated (known as copy number variants).[4]
- Genetic risk factors interact with environmental factors, including early insults to the developing brain (infection, hypoxia, starvation), psychosocial adversity and substance misuse, to produce psychotic disorders.[5]
- Psychotic disorders have a range of clinical presentations in terms of symptoms, functioning, course and response to treatments. This heterogeneity indicates that schizophrenia is not one single disease entity.[4]
- Changes in brain structure and function are found in most people with schizophrenia.
- Problems with neurocognition, such as processing speed and memory, and social cognition, such as recognising the emotions and motivations of other people, are common and are associated with social and role impairments.[4]
- Antipsychotics reduce psychotic symptoms in most people. However, there is a substantial minority (about 30%) in whom antipsychotics are not effective.[6]
- Clozapine is effective for most people with initially treatment resistant schizophrenia.[6]

- Psychological treatments such as cognitive behavioural therapy can reduce positive psychotic symptoms.[7]
- Treatment at multidisciplinary early intervention services in the early phase of illness is associated with improved outcomes.[8]
- Assertive community treatment and intensive case management is associated with improved service engagement, lower rates of hospitalisation and improved social functioning compared to treatment as usual.[9]

Gaps and uncertainties

Causes and aetiological mechanisms

Despite over one hundred years of research in schizophrenia and related psychotic disorders, and decades of research investigating biomarkers, the causes and aetiological mechanisms of psychotic disorders are still unknown.

Early intervention for psychosis services

Early intervention services (EI) for people in the early phase of illness can improve outcomes[8] and are cost-effective.[10] However the following knowledge gaps remain in relation to early intervention:

- Best models of care: Some gains from early intervention may be lost over time.[11,12] Therefore there is debate over whether these services should be extended, for example, from a typical 2 year tenure of care to a 5 year tenure.[13,14,15] The cost- effectiveness of extending tenure of care has not been examined.
- How to manage individuals who have suboptimal response to EI or fail to recover. This is especially the case for individuals with high levels of negative symptoms at baseline.[16,17]
- What the effective components of an EI service are. This is important for planning services where there are high budgetary constraints such as in low and middle income countries, but also has implications for Australia, for example if stepped down care is envisaged.

It is also now possible to identify individuals at high risk of developing a psychotic disorder through the use of standardised "Ultra High Risk" (UHR) criteria.[18] This opens up the possibility that psychosis could be prevented or at least delayed or its impact minimised in such individuals. While rates of psychosis onset in UHR individuals are several hundred fold above that of the general population, the majority of UHR individuals do not develop a psychotic disorder with a meta-analysis showing that the proportion is about 36% after 3 years.[19] Research to better predict those most at risk would enable more targeted treatment strategies. UHR individuals are also at risk of a range of other poor outcomes[20,21,22] and research to improve prediction and interventions targeted these other outcomes is also needed.

Treatment of positive symptoms of psychosis

Positive symptoms that do not improve with antipsychotic use: There is evidence that initial response to antipsychotics within 2 weeks is predictive of later response.[23,24] This suggests that clinicians should monitor and assess antipsychotic response frequently using a standardised system.[23] This would allow earlier consideration of the use of clozapine, which can be highly effective for individuals who have not shown an adequate response to other antipsychotics.[6] Despite this, there is evidence that clozapine is under-used.[25]

Positive symptoms not responsive to clozapine: As many as 40% of people with "treatment-resistant schizophrenia" do not respond to clozapine.[26] Augmentation with antipsychotics, antidepressants, mood-

stabilisers, anticonvulsants and glutamatergics has been trialled, as well as use of electro-convulsive therapy, transcranial stimulation and CBT.[6] However there is no clear evidence for the best treatment options in someone who is unresponsive to clozapine.

Psychological treatments: Cognitive behavioural therapy (CBT) can be used as an adjunct to pharmacotherapy. There is evidence that it has a small effect on positive symptoms and overall symptoms (general distress and low mood).[7,27] However it is not clear what factors best predict the most effective (and cost-effective) number of therapy sessions across different individuals and how therapy should be delivered for example, the role of e-health. The main research gap in relation to CBT for psychosis is how to improve its implementation into routine care. Despite being recommended in the Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines,[28] only about 22% of people with a psychotic disorder receive CBT in Australia.[29]

Treatment of negative symptoms

Negative symptoms have major impact on recovery and social and role functioning. They are highly prevalent in psychotic illnesses – in the Australian SHIP study over 85% of participants recorded at least one negative symptom.

However, they are poorly understood.[30] Their underlying aetiopathology is unknown, and there are no evidence based treatment for them. Antipsychotics, antidepressants, stimulants, including methylphenidate, d-amphetamine and modafinil, and anticonvulsants have all been trialled, but meta-anaylses suggest that they are not effective.[30] Small studies have shown some evidence of efficacy for agents that enhance NMDA receptor function such as d-serine and N-acetyl cysteine, but none were deemed to have clinically significant effects.[30]

Treatment of social cognition deficits

Deficits in social cognition, the processes involved in understanding social situations and other people, are common in people with psychotic disorders and are associated with difficulties in functioning. Psychosocial interventions are effective at reducing these deficits, including training to improve the recognition of other people's emotions and intentions of others.[31] What is unclear is whether these improvements can be sustained in the long term and whether they translate into better real-world functioning. In addition, not all people respond to training, and some approaches are more suitable to certain profiles than others. The identification of those most likely to benefit from different types of social cognitive intervention would enable a more personalized treatment approach and rational resource allocation.[31] Such research could lead to the more widespread implementation of these treatments.

Treatment of neurocognitive deficits

Impairment in cognition, such as in processing speed and memory, are common in psychotic disorders and generally precede the onset of positive psychotic symptoms.[32] Impaired cognition is associated with difficulties in functioning and thus is an important treatment target.[33] Pharmacological treatments, such as glutamanergic and cholinergic agents, have shown small effects but most are not sustained.[34] Psychosocial cognitive training programs, such as Cognitive Remediation, are associated with improved cognitive performance, symptoms, and psychosocial functioning[35] and can be administered via computer programs, enhancing their accessibility. Further research is needed to identify predictors of treatment response so that these interventions can be targeted to those most likely to respond. How this training can be implemented more widely within health services remains a challenge.

Additionally, physical exercise is associated with improvements in cognition in people with psychotic disorders.[36] Given that it has additional benefits for physical health and wellbeing,[37,38] it should be a priority to ensure that programs to promote exercise for individuals with psychotic disorders are available.

Physical health and premature mortality

Individuals with psychotic disorders have high rates of cardiovascular disease, respiratory diseases and Type 2 diabetes.[39,40,41,42] Their physical health is much worse than individuals with other mental disorders.[43] Despite this, compared to the general population, people with psychotic illnesses are less likely to receive timely and appropriate treatment for their physical health needs. Poor physical health also decreases well-being, reduces adherence with medication and hinders recovery from mental health symptoms. This adds to the social and economic burden of their mental illness.[44,45] Lifestyle interventions that increase physical activity, improve diet and decrease rates of smoking are effective in people with psychotic disorders with severe mental illness.[46,47] Research is needed into how to implement the effective components of lifestyle interventions across sectors and at scale.

Comorbid substance use

Comorbid substance use is common and can impede effective treatment and recovery in psychotic disorders. There is no robust evidence for any specific treatment approach.[48] One issue that impedes treatment of substance use problems is that there is often a separation between drug and alcohol and mental health services, with variable levels of collaboration between the two services.[28] Better integration of these services may improve access to treatments. Health service research into how this can be done in an effective, cost-effective and scalable way is needed.

Relapse prevention

Relapse following a first episode of psychosis is common.[49] Research into relapse prevention has mainly focused on antipsychotic medications, including strategies to improve adherence, use of long acting injectable medications and comparison of continuous versus intermittent medication use. Psychosocial strategies to reduce relapse risk have also been trialed, such as CBT and self-management strategies using early warning signs and family interventions.[23]

Another area of research is to identify factors that increase or decrease the risk of relapse so that treatment approaches can be more targeted.[50]

Support for families and carers

Families often play an important role in the recovery of people with mental health problems, yet they often receive little support. Family interventions have been trialled, with common elements found to be education about psychosis and enhancing coping strategies.[51] The research gap here is related to how these interventions can be implemented into routine care.

The role of peer workers

A small number of studies have explored the use of peer workers in mental health services but their effectiveness and cost-effectiveness have yet to be comprehensively evaluated.[28]

Vocational rehabilitation

There is evidence that supported employment is effective in improving vocational outcomes relevant to people with severe mental illness. The most effective form of supported employment is individual placement and support.[52] A major problem is translating evidence from research trials of vocational interventions into real-world improvements in employment rates.

Quality of life

Management of comorbid conditions: People with psychotic disorders have high rates of psychiatric comorbidities, including depression and anxiety disorders[53,54] and post-traumatic stress disorder.[54] These can have a major impact on quality of life. However, there is little evidence to guide the management of these conditions.[28]

Reducing stigma

Stigma in relation to mental illness is associated with delayed help-seeking, poor engagement with care, reduced self-esteem, self-efficacy, quality of life and hope and increased symptoms.[55] Interventions to reduce internalised stigma, such as psychoeducation, CBT and peer support, have shown promising results but a meta-analysis found no significant effect.[56] There are no specific interventions to reduce stigma recommended in RANZCP Clinical Practice Guidelines. Given the effect of internalised stigma on recovery and quality of life, more research is warranted into stigma reduction interventions.

SUMMARY BOX: Where more research is needed	
Evidence gaps	***Implementation gaps***
Causes and mechanisms of symptoms	Improving access to CBT, cognitive remediation, vocational rehabilitation and family support
Early psychosis: investigation of tenure of care in Early Intervention services; predictors of different outcomes in those at risk of psychosis	Improved access to exercise and other lifestyle interventions to improve physical health and cognition
Treatment research: positive symptoms unresponsive to clozapine; negative symptoms; impaired social cognition; comorbid disorders	Rational prescribing: early identification of non-response; more timely use of clozapine
Stigma reduction strategies	Better integration of alcohol and drug services and mental health services

Challenges

Definitions and boundaries of psychotic disorders

Better pathophysiological understanding of psychotic disorders is necessary to discover new treatment targets. However, the definition and boundaries of psychotic disorders and schizophrenia are not clear. The overlap and comorbidity with other disorders, delayed diagnoses and frequent poly-pharmacy also hinder biomarker research and make it difficult to distinguish causes and consequences of illness. Similarly, poor social and role functioning could be the result of stigma and social exclusion rather than the illness itself.

These issues create challenges for research into genetic and other biomarker research and hamper efforts to target treatments at underlying pathophysiological processes.

Implementing research evidence into practice

Implementation science and health services research is needed to investigate the best ways to change the behaviour of individuals (people with psychosis and clinicians), organizational practice and health systems in order to implement evidence into practice.

Lack of funding

A major barrier for mental health researchers is lack of research funding. Mental health research receives a lower proportion of NHMRC health funding compared with other National Health Priority Areas such as cancer, diabetes and cardiovascular disease, despite having the largest impact on the world economy and being a significant contributor to morbidity and mortality. Funding from philanthropy and non-government sources is also low compared to other disease areas.[57] In the latest NHMRC funding rounds there was a 60% decrease in mental health's share of projects. Less than 5% of NHMRC funding went to mental health research.

Psychotic disorders in particular seem to receive little attention from government and non- government funding agencies. For example, the Wellcome Trust charity has recently developed a major research focus on mental health but this is directed towards anxiety and depression.[58]

Opportunities

Opportunities to improve the connection between the research sector and the mental health services and supports sector

Psychosis research needs to be relevant to service users, carers and clinicians to ensure that the findings translate into improved health and wellbeing for those affected. The following are potential opportunities to achieve this:

- Ensuring that service users and carers are involved in a meaningful way in defining research priorities, research management and research practice.
- Improving the involvement of mental health clinicians in research. NHMRC clinical fellowships and similar schemes create an opportunity for this. Research needs to be seen as important to services to enable clinicians to work part time in research.
- Developing networks of researchers, clinicians, service users and carers will enable prioritising of research questions and may help with fund-raising for psychosis research. The Psychosis Australia Trust is such a body. However it needs more support from all sectors to be effective.[59]
- International and national research networks would allow more effective and innovative research to be conducted by bringing together researchers across disciplines and countries, and pooling expertise and data
- Use of routinely collected service data will enable some important research questions to be examined with minimal impact on service users and carers. Examples include use of service data to define outcomes for clinical trials and use of data to examine current practice and where this deviates from optimal practice.
- Development of a common national data set using the same measures for assessing symptoms, functioning and cognition will enhance the use of service data to answer important questions. This could be developed through networks of researchers, service users, carers and clinicians

- Use of linked State and Federal data will enable examination of large cohorts to study patterns in trajectories and their links to social determinants and treatments.

Enablers of future research

- Commitments from decision-makers about the importance of psychosis research, given the extent of the issue worldwide and its impact of individuals and families
- Funding from government and non-government bodies – for research and development of networks
- Shift in public attitudes may shift policies, highlight the importance of psychosis research and increase funding
- Support from service users, carers, clinicians and health service managers for use of routinely collected service data would assist in obtaining ethical support for research
- Novel technologies such as use of smart phones to collect data and deliver interventions could also enable future research

Research priorities

The following have been named as the top challenges by the Psychosis Australia Trust (PAT) following a 2018 consultation exercise with service users, carers and clinicians, and by the participants of the 2010 Survey of High Impact Psychosis (SHIP) study.[29]

Top challenges for people with psychosis	
PAT	***SHIP***
Improved life expectancy and physical health	Improved finances and employment
Improved cost-effective treatments	Decreasing loneliness and social isolation
Improved quality of life	Improved physical health
Increased social and economic participation, including employment	Improved mental health symptoms
Prevention and cure of psychotic disorders	Better housing conditions

As can be seen, there are areas of considerable overlap between these two surveys: physical health, employment, quality of life and better treatments to improve mental health symptoms all feature as high priorities for both groups. Research focussing on these areas should therefore be supported.

Conclusion

Australia is world leading in psychosis research (see http://expertscape.com/ex/psychotic+disorders). To ensure that such high quality research continues it is imperative that the Federal Government financially supports research studies and researchers to continue their work and to grow the next generation of researchers.

Research to improve the health, well-being and quality of life of people with psychotic disorders should be a national priority.

A lot of evidence already exists about how to improve some key areas identified by service users. The gap in knowledge is how to ensure such evidence is translated into practice and policy change. Examples include improving physical health, access to psychological therapies and vocational support. Major evidence gaps remain in our understanding of the causes of psychotic disorders, treatment for negative symptoms and

refractory positive symptoms and stigma reduction. Reduction of stigma would improve social isolation and social and economic participation.

Access to large routinely collected data sets would provide opportunity to increase the productivity of research. Funding for the development of networks of researchers, clinicians, service users and carers would drive psychosis research forward.

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