ANZJP

Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders

Cherrie Galletly[1,2,3], David Castle[4], Frances Dark[5],
Verity Humberstone[6], Assen Jablensky[7], Eóin Killackey[8,9],
Jayashri Kulkarni[10,11], Patrick McGorry[8,9,12],
Olav Nielssen[13] and Nga Tran[14,15]

Abstract

Objectives: This guideline provides recommendations for the clinical management of schizophrenia and related disorders for health professionals working in Australia and New Zealand. It aims to encourage all clinicians to adopt best practice principles. The recommendations represent the consensus of a group of Australian and New Zealand experts in the management of schizophrenia and related disorders. This guideline includes the management of ultra-high risk syndromes, first-episode psychoses and prolonged psychoses, including psychoses associated with substance use. It takes a holistic approach, addressing all aspects of the care of people with schizophrenia and related disorders, not only correct diagnosis and symptom relief but also optimal recovery of social function.

Methods: The writing group planned the scope and individual members drafted sections according to their area of interest and expertise, with reference to existing systematic reviews and informal literature reviews undertaken for this guideline. In addition, experts in specific areas contributed to the relevant sections. All members of the writing group reviewed the entire document. The writing group also considered relevant international clinical practice guidelines. Evidence-based recommendations were formulated when the writing group judged that there was sufficient evidence on a topic. Where evidence was weak or lacking, consensus-based recommendations were formulated. Consensus-based recommendations are based on the consensus of a group of experts in the field and are informed by their agreement as a group, according to their collective clinical and research knowledge and experience. Key considerations were selected and reviewed by the writing group. To encourage wide community participation, the Royal Australian and New Zealand College of Psychiatrists invited review by its committees and members, an expert advisory committee and key stakeholders including professional bodies and special interest groups.

[1]Discipline of Psychiatry, School of Medicine, The University of Adelaide, SA, Australia
[2]Ramsay Health Care (SA) Mental Health, Adelaide, SA, Australia
[3]Northern Adelaide Local Health Network, Adelaide, SA, Australia
[4]Department of Psychiatry, St Vincent's Health and The University of Melbourne, Melbourne, VIC, Australia
[5]Rehabilitation Services, Metro South Mental Health Service, Brisbane, QLD, Australia
[6]Mental Health and Addiction Services, Northland District Health Board, Whangarei, New Zealand
[7]Centre for Clinical Research in Neuropsychiatry, School of Psychiatry and Clinical Neurosciences, The University of Western Australia (UWA), Crawley, WA, Australia
[8]Orygen – The National Centre of Excellence in Youth Mental Health, Parkville, VIC, Australia
[9]The University of Melbourne, Melbourne, VIC, Australia
[10]The Alfred Hospital and Monash University, Clayton, VIC, Australia
[11]Monash Alfred Psychiatry Research Centre, Melbourne, VIC, Australia
[12]Board of the National Youth Mental Health Foundation (headspace), Parkville, VIC, Australia
[13]Psychiatry, Northern Clinical School, The University of Sydney, Sydney, NSW, Australia
[14]St Vincent's Mental Health, Melbourne, VIC, Australia
[15]Department of Psychiatry, The University of Melbourne, Melbourne, VIC, Australia

Corresponding author:
Cherrie Galletly, The Adelaide Clinic, 33 Park Terrace, Gilberton, SA 5081, Australia.
Email: cherrie.galletly@adelaide.edu.au

guide.medlive.cn

Results: The clinical practice guideline for the management of schizophrenia and related disorders reflects an increasing emphasis on early intervention, physical health, psychosocial treatments, cultural considerations and improving vocational outcomes. The guideline uses a clinical staging model as a framework for recommendations regarding assessment, treatment and ongoing care. This guideline also refers its readers to selected published guidelines or statements directly relevant to Australian and New Zealand practice.

Conclusions: This clinical practice guideline for the management of schizophrenia and related disorders aims to improve care for people with these disorders living in Australia and New Zealand. It advocates a respectful, collaborative approach; optimal evidence-based treatment; and consideration of the specific needs of those in adverse circumstances or facing additional challenges.

Keywords
Schizophrenia, schizoaffective, first-episode psychosis, management, treatment

Off-label prescribing

In this guideline, evidence and expert opinion for the effectiveness of treatments for schizophrenia and related disorders have been reviewed and considered. In some instances, the therapies (e.g. medicines) identified as effective may not be specifically approved for such use in Australia and/or New Zealand.

The use of such therapeutic agents outside their approved indication(s) is sometimes referred to as 'off-label' use, and in practice, this may impact eligibility for third-party payer subsidy. We recommend careful documentation supporting your clinical use of specific therapeutic agents over alternatives that are approved in your country. It is also recommended that this issue is explained to patients, including informing them that they may personally have to meet added costs due to lack of third-party payer subsidy.

Introduction

This clinical practice guideline (CPG) was developed on behalf of the Royal Australian and New Zealand College of Psychiatrists (RANZCP). It updates the previous RANZCP CPG for the management of schizophrenia and related disorders (McGorry et al., 2005). It takes into account the findings of new research published since the previous edition and reflects an increasing emphasis on early intervention, physical health, psychosocial treatments and improving vocational outcomes.

It is important to acknowledge the extraordinary courage and perseverance shown by many people with schizophrenia, who often live with the burdens of symptoms, stigma, social exclusion and socioeconomic disadvantage. Their families and carers also face significant ongoing challenges.

Scope and purpose

This guideline provides recommendations for the clinical management of schizophrenia and related disorders for health professionals working in Australia and New Zealand.

It aims to encourage all clinicians to adopt best practice principles. The recommendations represent the consensus of a group of Australian and New Zealand experts in the management of schizophrenia and related disorders.

It is intended mainly for psychiatrists, psychiatry trainees, resident medical officers and hospital interns in psychiatry. It may also be useful to general practitioners (GPs), mental health nurses, other clinicians who work with people with schizophrenia and related psychoses, and policy makers. It does not override the responsibility of clinicians to make appropriate decisions, taking into account the unique circumstances of the person they are treating.

The scope of this guideline is the schizophrenia spectrum which includes schizophrenia, schizoaffective disorder, schizotypal disorder, schizophreniform disorder and acute transient psychotic disorder with symptoms of schizophrenia. The spectrum notion is based on the presumption (and partial evidence) of a shared genetic background. Notably, persistent delusional disorder is not part of the spectrum. This guideline includes the management of ultra-high risk syndromes, first-episode psychoses (FEPs) and prolonged psychoses, including psychoses associated with substance use. Childhood onset schizophrenia, a very rare condition requiring specialist management, is not included. The prescription of antipsychotic drugs for conditions other than schizophrenia and related disorders is also beyond the scope of this CPG. Psychoses associated with affective disorders are covered in the RANZCP CPG on mood disorders (Malhi et al., 2015). This CPG does not include detailed information about mental state examination, diagnostic criteria and differential diagnosis – these matters are covered in textbooks and manuals of diagnostic criteria.

Method

Developing the recommendations and commentary. The working group planned the scope and individual members drafted sections according to their area of interest and expertise, with reference to existing research literature and reviews. In addition, experts in specific areas contributed to the relevant

sections. The working group considered recent international CPGs, including the UK National Institute for Health and Care Excellence (NICE) (2014) clinical guideline on the treatment and management of psychosis and schizophrenia in adults and the World Federation of Societies of Biological Psychiatry guidelines for the biological treatment of schizophrenia (Hasan et al., 2012, 2013, 2015; Thibaut et al., 2015). The staging model (McGorry et al., 2006) provided a framework for assessment and clinical management and for the choice and timing of interventions.

For intervention studies, levels of evidence were assigned according to Australian National Health and Medical Research Council (NHMRC) (2009b) levels of evidence (Table 1).

Evidence-based recommendations (EBRs) were formulated when the working group judged that there was sufficient evidence on a topic. For each EBR, the number indicates the level of evidence on which the recommendation was based. Where evidence was weak or lacking, consensus-based recommendations (CBRs) were formulated. CBRs are based on the consensus of a group of experts in the field and are informed by their agreement as a group, according to their collective clinical and research knowledge and experience. Where applicable, key considerations were selected from the recommendations on each topic.

The whole working group reviewed the entire manuscript, and discussion occurred via a series of teleconferences. Where members disagreed about clinical advice or interpretation of evidence, the issue was discussed until consensus was reached.

This guideline also refers readers to selected current documents, statements or algorithms that have been published elsewhere. These were either developed in Australasia or by expert groups led by, or including, Australasian experts.

Expert review and public consultation. A draft version of this guideline was reviewed by experts in schizophrenia (clinical and academic) from Australia and New Zealand, between 1 July and 25 July 2014. A total of 11 expert advisers provided their feedback. The working group considered all reviewers' comments and revised the manuscript in response to their suggestions.

A revised version of the guideline was released for public consultation between 2 February and 5 March 2015. During the consultation period, the draft guideline was publicly available on the RANZCP website. To encourage wide community participation, RANZCP invited review by key stakeholders including RANZCP Fellows and trainees, professional bodies, special interest groups and consumer and carer groups. The reviewers were asked to respond via an online survey, which asked the following four questions for each section of the guideline:

- Are there any significant gaps (of topic, literature, other)?

Table 1. NHMRC levels of evidence for intervention studies.

Level	Design
I	A systematic review of level II studies
II	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: • Non-randomised, experimental trial • Cohort study • Case-control study • Interrupted time series with a control group
III-3	A comparative study without concurrent controls: • Historical control study • Two or more single-arm studies • Interrupted time series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes

Source: National Health and Medical Research Council (NHMRC, 2009b).

- Are there errors in the content?
- Is the structure logical and easy to use?
- Do you have any other comments?

Key stakeholders who provided feedback are listed in the 'Acknowledgements' section. The working group considered all feedback received from the expert advisers and broader consultation process and modified the draft where necessary. The revised draft was then reviewed by the following RANZCP committees:

- Committee for Therapeutic Interventions and Evidence-Based Practice
- Practice, Policy and Partnership Committee
- Corporate Governance and Risk Committee.

Several amendments were made and final draft was sent to the RANZCP Board in October 2015 for approval. The approved draft was sent to the *Australian & New Zealand Journal of Psychiatry* (ANZJP) for peer review and publication.

Expert advisors, professional bodies and special interest groups are listed in the 'Acknowledgements' section.

Declaration of interests. Members of the schizophrenia CPG working group were required to sign a deed of undertaking at the time of appointment, in which they agreed to declare any conflict, whether actual, potential, perceived or likely to arise in matters considered by the working group.

The process for management of conflict of interest (COI) was detailed in the working group terms of reference: as part

guide.medlive.cn

of the standing items of any meeting, declarations of COI were called for and minuted. Once a COI had been declared, the individual concerned could be excluded from the discussion at the discretion of the Chair.

The working group members signed an updated COI form at the time of submitting the guideline for publication. All members and their declaration of interests are listed in Appendix 1.

Background

What is schizophrenia? Schizophrenia is a complex disorder of brain function with wide variation in symptoms and signs, and in the course of the illness. The experiential '*core*' of schizophrenia has been described as a '*disturbance involving the most basic functions that give the normal person a feeling of individuality, uniqueness and self-direction*' (World Health Organization [WHO], 1992). The deficits in neurological, psychological and social function that manifest in the various syndromes of schizophrenia appear to have a number of genetic and environmental causes.

Schizophrenia is the most common and most important disorder within a spectrum of clinically similar (and possibly genetically related) conditions, which include schizoaffective disorder, schizotypal disorder and acute transient psychotic disorders (Jablensky, 2006). The term 'schizophrenia' includes a range of clinical presentations and personal experiences that result from complex interactions between genes and the environment, and are influenced by the person's reaction to their experience of the disorder.

Variation in the incidence and prevalence of schizophrenia between populations is greater than was once believed (Simeone et al., 2015). As many as 1% of people meet diagnostic criteria for the disorder over their lifetime. Schizophrenia often has profound effects on people with the disorder and their families. In terms of the global burden of disease and disability, schizophrenia ranks among the top 10 disorders worldwide (Mathers and Loncar, 2006).

Clinical presentation and diagnosis. There is currently no validated biological marker of schizophrenia. The diagnosis is made by identifying the symptoms and signs of the disorder, which include delusional beliefs, hallucinations, disorganised thinking and speech, cognitive impairment, abnormal motor behaviour and negative symptoms. While neuroimaging and cognitive testing may help to rule out alternatives, such as schizophrenia-like manifestations of other disorders affecting brain function, schizophrenia is essentially a clinical diagnosis. The syndrome of schizophrenia, as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD) classification systems, can be diagnosed with a high degree of inter-rater reliability. However, the validity of the syndromal diagnosis is currently under examination due to the variation in the course and clinical presentation of the disorder.

Since the onset of psychotic symptoms is often preceded by a prolonged period of disturbance of cognition, affect and behaviour, the importance of a thorough exploration of the person's developmental history and premorbid personality cannot be overestimated. Among the presenting symptoms, those of particular importance for the diagnosis include persistent delusions and hallucinations, incongruent or blunted affect, and interruptions in the train of thought. Characteristic 'first-rank' symptoms (thought insertion, withdrawal or broadcasting, hallucinatory voices commenting on the person's behaviour and passivity experiences) may be present, but are not pathognomonic for schizophrenia. Depressive symptoms and anxiety are common. In differential diagnosis, one should consider other primary psychotic disorders as well as a range of neurological and systemic medical conditions (Cardinal and Bullmore, 2011; Freudenreich et al., 2009). The differentiation of schizophrenia from substance-induced psychotic disorders may be particularly difficult and should be based on a careful review of the temporal relationship between drug taking and the emergence and persistence of psychotic symptoms (see '*Section 2. Comorbid substance use*').

Aetiology and pathogenesis. Schizophrenia is a complex, multifactorial disorder. Its aetiology has a major genetic component involving multiple genes of small effect, individual assortments of rare mutations (copy number variations) and molecular pathways that are likely to be heterogeneous, both within and across populations (Sullivan et al., 2012). Environmental factors, ranging from neurodevelopmental insults (e.g. maternal pregnancy complications and birth complications) to psychosocial adversity and substance misuse, interact with genetic susceptibility to produce widespread phenotypic variation (Demjaha et al., 2012; Gottesman and Bertelsen, 1989). The '*social defeat*' hypothesis draws together various environmental risk factors to explain how they might lead to schizophrenia (Selten et al., 2013). Precursors of schizophrenia, including developmental delays, cognitive abnormalities, attenuated symptoms and odd behaviour, may appear very early in life. However, such developmental precursors – if they occur – are usually subtle and are not specific indicators of subsequent psychosis.

Most research into schizophrenia is based on the highly unlikely assumption that schizophrenia is a single, uniform disorder. Research into the various forms of schizophrenia has been assisted by the conceptual tool of endophenotypes, which are heritable, objectively measurable biological traits that co-segregate with clinical illness in pedigrees and may also be expressed in unaffected members. Endophenotypes include distinct patterns on neuropsychological tests of cognitive function, brain electrophysiological measures and neuroimaging variables (Thibaut et al., 2015). Measures of cognitive deficit, including deficits in memory and attention, executive function and sensory

gating, have been shown to be particularly sensitive to the dysfunction that sets people with schizophrenia apart from healthy controls (Nuechterlein et al., 2012).

Prevalence, incidence and lifetime risk. Much has been learnt in recent years about the epidemiology of schizophrenia. As one would expect for a heterogeneous group of disorders, frequency estimates related to the incidence and prevalence of schizophrenia vary (McGrath et al., 2004; Saha et al., 2005). Some variation can be attributed to study methodology, but high-quality multicentre studies show significant variation in the incidence of schizophrenia between nations (Sartorius et al., 1986) and within nations (Kirkbride et al., 2006). The incidence of schizophrenia is higher in men than in women; the ratio of males to females is 1.4 to 1 (Aleman et al., 2003; McGrath et al., 2008). Some migrant groups have substantially higher risks of schizophrenia (Bourque et al., 2011; Cantor-Graae and Selten, 2005), and people born and raised in urban areas have an increased risk of schizophrenia, compared with those born and raised in rural settings (Vassos et al., 2012).

Two Australian nationally representative surveys produced very similar estimates of the treated annual prevalence of broadly defined psychotic disorders among people in contact with mental health services: 4.0 per 1000 in 1997–1998 (Jablensky et al., 2000) and 4.5 per 1000 in 2010 (Morgan et al., 2012). With respect to schizophrenia (a subgroup of the psychotic disorders), the estimated lifetime morbid risk (age range 18–45) is 2.37 per 1000 population (Morgan et al., 2014). The frequency of schizophrenia in Australian Indigenous communities is unknown, but higher rates of admission to psychiatric hospitals, as well as the effects of pervasive social disadvantage, suggest that the prevalence may be higher among Aboriginal people than in the wider society (Hunter, 2013). The prevalence of schizophrenia is thought to be elevated among Māori (Kake et al., 2008). An understanding of the social and cultural contexts of schizophrenia and related disorders among Aboriginal and Torres Strait Islander peoples and Māori is essential for planning clinical care (see '*Section 5. Specific populations and circumstances*').

Course and outcome. The course of schizophrenia is variable. At least three domains that do not co-vary over time need to be independently assessed: symptom severity, functional impairment (including cognitive deficits) and social and occupational disability. The onset is usually in adolescence and early adult life, coinciding with a developmental stage of incomplete social maturation, educational attainment and acquisition of occupational skills (see '*Section 1. The stages of schizophrenia: a framework for clinical care*'). The intrusion of psychosis at this stage may result in a severely truncated repertoire of social skills, and disrupted vocational and developmental trajectory, which can create lifelong socioeconomic disadvantage and failure to achieve

the person's full potential. Both the positive and negative symptoms of the disease can interfere with the person's capacity to cope with the expectations of daily life. People with schizophrenia experience particular cognitive difficulties in dealing with complex demands and environments, especially those that involve social interaction. These difficulties can be exacerbated by the societal reaction to individuals manifesting aberrant behaviours, which includes stigma and social exclusion. Interactions between these adverse factors can cause the '*social breakdown syndrome*' (Gruenberg, 1974) – the cluster of secondary and tertiary impairments in schizophrenia that result in a loss of social support networks and greatly diminished quality of life.

A meta-analysis of 320 studies published between 1895 and 1992 with a total of 51,800 subjects (Hegarty et al., 1994) showed that approximately 40% of people with schizophrenia were reported as improved after a mean follow-up of 5.6 years. A significant increase in the rate of improvement has occurred since the 1960s, likely due to the introduction of antipsychotic medications. Two major, multicentre prospective follow-up studies by the WHO (Hopper et al., 2007; Jablensky et al., 1992) found striking differences between countries in the course and outcome of schizophrenia, but overall, more than 30% had relatively favourable clinical outcomes after 15 and 25 years of follow-up. A long-term follow-up study of people presenting with first-episode schizophrenia showed that about half had good outcomes, and 16% of people with early, unremitting symptoms achieved late-phase recovery (Harrison et al., 2001). There is emerging evidence that early detection and treatment are associated with a better long-term outcome (Craig et al., 2004; Ten Velden Hegelstad et al., 2012).

A 2010 Australian national survey (Morgan et al., 2014) revealed that 6% of participants with schizophrenia experienced a single episode of psychosis followed by good recovery, 54.8% experienced multiple episodes with good or partial recovery between the episodes, and 38.8% of participants showed an unremitting continuous course with deterioration. Despite the high risk of chronic disability, loss of developmental potential and diminished quality of life associated with schizophrenia, and despite widespread neglect of the care of people with schizophrenia around the world, about one in seven of those who meet the diagnostic criteria for schizophrenia ultimately attain nearly complete recovery (Jaaskelainen et al., 2013). Predictors of recovery include a higher level of premorbid occupational achievement and social competence, lower likelihood of substance use, better insight and a sense of an internal '*locus of control*' (Hopper et al., 2007). The possibility of complete recovery justifies an optimistic approach, not only early in the course of illness but also in people with persistent, chronic symptoms and disability.

Comorbidity and mortality. Schizophrenia is associated with excess mortality, which has been well documented by

guide.medlive.cn

epidemiological studies on large cohorts over extended periods. Standardised mortality ratios (SMRs) of 2.6 or higher have been reported, which correspond to a reduction in life expectancy of approximately 20% (Chwastiak and Tek, 2009; Saha et al., 2007). Laursen (2011) found a reduction in life expectancy of 18.7 years for men and 16.3 years for women with schizophrenia. The leading causes of premature death among people with schizophrenia are cardiometabolic diseases, suicide and accidents (Laursen, 2011).

The second Australian National Survey of Psychosis (Cooper et al., 2012) estimated the prevalence of tobacco smoking among people with schizophrenia at 71% in men and 59% in women – more than three times higher than in the general population. Substance use is the most common comorbid health problem (Moore et al., 2012); the addictive use of cannabis, stimulants and nicotine is disproportionately high among people with psychosis and may be related to the underlying neurobiology of the disorder.

Suicide accounts for 28% of the excess mortality in people with schizophrenia, with aggregated SMR of 9.6 for men and 6.8 for women (Saha et al., 2007). Several risk factors have been suggested that are relatively specific to schizophrenia: the combination of young age and male sex, high level of education, the presence of insight, family history of suicide, substance use and the presence of depressive symptoms, hallucinations and delusions (Hor and Taylor, 2010). In an Australian study (Lawrence et al., 2000), the highest suicide risk was found in the first 7 days after discharge from inpatient care.

Social and economic costs. The social and economic costs of schizophrenia are disproportionately high, relative to its incidence and prevalence. Schizophrenia is associated with a greater burden of long-term disability than any other mental disorder.

Recent evidence from epidemiological, clinical and neurobiological research reinforces the view that people affected by schizophrenia are highly responsive to the social environment and that progressive social exclusion is a major contributor to their disablement, low self-esteem and apathy. Deficits caused by the disorder become amplified by environmental factors, resulting in loss of peer networks and social support, loss of meaningful goals and role fulfilment, disuse of acquired skills and knowledge, and downgrading of attitudes and expectations. Keeping people with schizophrenia socially engaged, especially by facilitating their participation in the workforce through supported employment, is one of the most effective strategies for countering social exclusion.

In most developed countries, the direct costs of schizophrenia (incurred by hospital or community-based treatment, supervised accommodation and related services) amount to 1.4–2.8% of national health care expenditure and up to 20% of the direct costs of all mental health conditions.

The indirect costs are likely to be comparable in scale to the direct costs, considering lost productivity and employment and the economically devastating long-term impact of the illness on families and other caregivers. A detailed analysis of the differences between the first (1997–1998) and second (2010) Australian National Survey of Psychosis revealed minimal change in the overall average annual costs, but a significant redistribution of specific expenditures (Neil et al., 2014). This change was broadly related to the reforms driven by the National Mental Health Plan (Australian Government Department of Health, 2009), which prioritised community-based outpatient care and services provided by the non-governmental organisation (NGO) sector. There were significant increases in the average annual cost for outpatient care (increased by AUD$7,380 per person): NGO services (increased by AUD$2,448 per person) and pharmaceuticals (increased by AUD$1,892 per person). These increases were offset by a significant reduction of inpatient costs (reduced from AUD$22,715 to AUD$10,925 per person) and a 6.5-fold decrease in NGO crisis accommodation costs (reduced by AUD$604 per person).

However, productivity losses (the greatest component cost) did not change, indicating the constancy of low employment levels of people with schizophrenia. The proportion of individuals receiving government income support remained at 85%. Given that most people with schizophrenia are smokers and regularly purchase tobacco products, there is little money available for clothing, food, transport and recreational activities. The lack of improvement in workforce participation is very disappointing, given that many people with schizophrenia express a desire to work, and most likely reflects a failure to develop effective vocational rehabilitation services. Improved vocational outcomes would have economic benefits, as well as improving social inclusion and quality of life.

Early intervention for psychotic disorders has been shown to be cost-effective (Hastrup et al., 2013; McCrone et al., 2009). Further research is needed in this area.

Legal, forensic and ethical issues. People with schizophrenia face higher rates of incarceration than the general population, sometimes for violence but also for trivial offences. They are also more likely to be victims of crime. The relationship between psychosis and violence is complex. Delay in the diagnosis and treatment of FEP and loss of continuity of care of people with disturbing symptoms and comorbid substance use have been shown to contribute to episodes of violence (Nielssen et al., 2012). The balance between personal rights, the propensity to harm others and recognition of the need for treatment are the main considerations in decisions to provide involuntary treatment (see '*Involuntary treatment*' in '*Section 3. Treatment: context, structure and content of interventions*').

guide.medlive.cn

Section 1. The stages of schizophrenia: a framework for clinical care

The concept of staging

Staging is routine for many medical conditions. Over the last decade, a clinical staging model for mental illnesses has been developed (McGorry et al., 2006), which proposes that the course of illness is a continuum (Table 2). Clinical staging models assume that treatments offered earlier in the course of an illness have the potential to be safer, more acceptable, more effective and more affordable than those offered later. Interventions can be evaluated in terms of their ability to prevent or delay progression from earlier to later stages of illness, and can be selected by the individual with schizophrenia and their clinicians on the basis of defined risk/benefit criteria.

At all stages, the therapeutic relationship is the foundation of clinical care. Time must be spent building trust and good communication. This is just as important for people with unremitting illness, as it is for those early in the course of the disorder. It is essential to take a respectful approach, provide accurate information and address the person's questions and concerns. People with thought disorder, or other difficulties with conversation, are generally capable of meaningful communication and will often appreciate the opportunity to express their point of view and participate in clinical decision-making (Galletly and Crichton, 2011).

Comorbid substance abuse, which is very common among people with schizophrenia, can complicate the presentation and worsen outcomes (see '*Section 2. Comorbid substance use*').

The pre-psychotic or prodromal stage (stages 1a, 1b)

Before the emergence of positive psychotic symptoms that are sufficiently severe and persistent to justify a diagnosis of schizophrenia or FEP, most people show a prolonged period of symptoms and increasing disability. This is commonly termed the 'prodrome' in retrospect, and the 'ultra-high-risk mental state' or 'at-risk mental state' prospectively. The pre-psychotic or prodromal stage is associated with evidence of changes in brain structure, probably reflecting active neurobiological processes (Tognin et al., 2014). The neuropathological basis of these changes remains unclear.

A 2012 meta-analysis (Fusar-Poli et al., 2012) showed that among people identified as being at high risk of psychosis, rates of transition to psychosis were 22% at 1 year and 36% at 3 years. However, prediction of transition to psychosis is unreliable and some recent studies show transition rates under 10%. Those who do not transition to psychosis mostly have mood/anxiety disorders, which need appropriate treatment (Fusar-Poli et al., 2013; Lin et al., 2012).

The potential benefits of identifying and proactively treating individuals at risk of psychosis are significant because much of the psychosocial disability that becomes entrenched in the subthreshold period, prior to FEP, is difficult to reverse even when the core symptoms remit with effective treatment. People are also at risk of suicidal behaviour during the pre-psychotic or prodromal stage (Kelleher et al., 2013).

The ultra-high risk or at-risk mental state typically affects young people, usually aged between 14 and 35 years. It is characterised by a change in subjective experience and behaviour that is persistent and often progressive (although

Table 2. Clinical stages of schizophrenia and related disorders.

Clinical stage	Definition
0	Increased risk of psychosis No symptoms currently
1a	Mild or non-specific symptoms of psychosis, including neurocognitive deficits Mild functional change or decline
1b	Ultra-high risk of psychosis Moderate but subthreshold symptoms, with moderate neurocognitive changes and functional decline to caseness or chronic poor function (30% drop in SOFAS in previous 12 months or <50 for previous 12 months)
2	First episode of psychotic disorder: full-threshold disorder with moderate-to-severe symptoms, neurocognitive deficits and functional decline (GAF 30–50) Includes acute and early recovery periods
3a	Incomplete remission from first episode of care
3b	Recurrence or relapse of psychotic disorder that stabilises with treatment, but at a level of GAF, residual symptoms or neurocognition below the best level achieved following remission from the first episode
3c	Multiple relapses with objective worsening in clinical extent and impact of illness
4	Severe, persistent or unremitting illness, as judged by symptoms, neurocognition and disability criteria

Source: Adapted from McGorry et al. (2006).
SOFAS: social and occupational function assessment scale; GAF: global assessment of function.

guide.medlive.cn

it may fluctuate in severity), together with either of the following:

- Subthreshold positive symptoms that are not severe or persistent enough to be regarded as evidence of sustained frank psychosis sufficient for a diagnosis of a psychotic disorder (other than brief psychotic episode) according to the *Diagnostic and Statistical Manual of Mental Disorders–Fifth Edition* (DSM-5) criteria (American Psychiatric Association, 2013).
- A family history of psychotic disorder or schizotypal disorder in a first-degree relative, plus a significant yet non-specific decline in psychosocial function within the past year or so that is not resolving.

In addition, to meet ultra-high risk criteria, there must be a functional decline to caseness or chronic poor function (30% drop in the Social and Occupational Functioning Assessment Scale in previous 12 months or score < 50 for previous 12 months).

Intervention during the pre-psychotic stage has several potential benefits:

- Intervention may prevent or lessen social disability, which can develop during this stage.
- Engagement with mental health professionals can occur while the individual is not experiencing acute illness (Yung, 2003).
- Trauma and stigma might be lessened because there is less risk of acute behaviour problems or embarrassing behaviour, and less need for hospitalisation. However, this consideration needs to be balanced against the potential risk of self-stigmatisation, especially when a false positive diagnosis is made (Malla and Norman, 2002).

- The duration of untreated psychosis might be reduced; if FEP does occur, it can be recognised rapidly in well-engaged individuals.
- Transition to FEP may be delayed or prevented (Van der Gaag et al., 2013).

These potential benefits need to be balanced against the potential risks of overtreatment and 'labelling'.

There is a considerable body of research examining the effectiveness of treatments during the pre-psychotic phase. A number of randomised controlled trials (RCTs) have investigated whether interventions can prevent or delay transition to psychosis in a proportion of people at risk (Van der Gaag et al., 2013). Interventions that have been evaluated include cognitive behaviour therapy (CBT), antipsychotic medication, a combination of CBT and antipsychotic medication, an intensive treatment that included family intervention, and fish oil supplementation (Stafford et al., 2013). There is evidence that transition to psychosis can be delayed (Van der Gaag et al., 2013), and further clinical trials, with longer follow-up periods, are needed to ascertain whether transition can be completely averted. Meanwhile, early intervention for people who meet criteria for an ultra-high risk mental state should be supported. Besides the obvious benefits to the individual, their family, and the wider community, there are also economic advantages to preventing transition to psychosis (Ising et al., 2015).

FEP (stage 2)

FEP is defined as 1 week or more of sustained positive symptoms above the psychosis threshold for delusions and hallucinations in particular. There are a range of diagnoses captured here with about 60% falling within the schizophrenia

Recommendations on the management of the pre-psychotic or prodromal phase	Type	Level of evidence
The possibility of psychotic disorder should be considered for any young person who is experiencing unexplained functional decline.	EBR	I
If subthreshold psychotic features combined with the onset of disability indicating ultra-high risk are present, the young person and their relatives should be assessed and mental state and safety monitored regularly (every 2–4 weeks), in a context of ongoing support, until recovery or transition. CBT is the preferred intervention.	EBR	I
Syndromes such as depression and substance use, and problem areas such as interpersonal, vocational and family stress should be appropriately managed.	EBR	I
Information about the level of risk should be provided carefully to the young person and their family, taking into account social, educational and cultural factors.	EBR	III-1
Antipsychotic medicines should not normally be prescribed unless frank positive psychotic symptoms have been sustained for at least 1 week. The exception may be where briefer or milder positive symptoms are directly associated with risk of self-harm or aggression (e.g. in substance-related psychotic disorder), or when subthreshold positive psychotic symptoms persist despite CBT and other psychosocial treatments and are causing distress and/or disability.	EBR	III-1

CBT: cognitive behaviour therapy; EBR: evidence-based recommendation.

guide.medlive.cn

spectrum at this point although more 'graduate' later. The purposes of early intervention in FEP are to ensure the safety of the young person and others, to reduce the duration of untreated psychosis as much as possible and to preserve and restore function, thereby reducing the disability associated with psychotic illness. Management of FEP requires a holistic, systematic approach which involves a comprehensive range of pharmacological and psychosocial interventions. More comprehensive information is available at www.ranzcp.org/Publications/Guidelines-for-clinical-practice/Schizophrenia-early-psychosis-resources.aspx. There is evidence for the cost-effectiveness of specialised early psychosis services (Hastrup et al., 2013; Park et al., 2014).

A comprehensive assessment including physical health screening (Table 3) is essential (Freudenreich et al., 2009).

Duration of untreated psychosis. While there has been debate about the impact of the duration of untreated psychosis (Killackey and Yung, 2007), this has been shown to be an independent predictor of outcome (Penttilä et al., 2014). Reducing the duration of untreated psychosis is, therefore, an important aim. Research has shown that combining awareness-raising campaigns with a readily available FEP service leads to a significant reduction in the duration of untreated psychosis (Joa et al., 2008).

Managing the critical period. People experiencing a first episode of psychosis need comprehensive treatment that continues throughout the entire critical period. The critical period is defined as the first 5 years for a subset of people (Birchwood and Fiorillo, 2000). For all others, there is international consensus that treatment should continue for at least 2 years (Orygen Youth Health Research Centre, 2011).

The OPUS study in Denmark compared people accessing a FEP service with those receiving standard care. There were significant differences between groups in favour of intervention at the end of the 2-year treatment period (Thorup et al., 2005). After the 2 years of specialised first-episode treatment, participants transferred to standard care, and when these participants were followed up at 5 years, most of the gains made at the 2 year assessment had been lost (Bertelsen et al., 2008). It has been shown that longer term (5 years) continuity of care within a specialised early intervention programme is associated with continuing benefits (Norman et al., 2011) and that FEP services can achieve gains that are still measurable 10 years later (Ten Velden Hegelstad et al., 2012).

Prescribing considerations. A treatment algorithm for pharmacological treatment for first-episode non-affective psychosis is provided in Figure 1.

Young people are particularly sensitive to the side effects of psychotropic medicines. A low starting dose with gradual titration up to an effective level is recommended, unless the young person is acutely mentally ill and requires urgent treatment. Second-generation antipsychotic agents (SGAs) are recommended in preference to first-generation antipsychotic

Table 3. Physical assessment and investigations for people presenting with first-episode psychosis.

Physical examination including neurological examination
Full blood count and ESR
Electrolytes, liver function tests
Fasting glucose, cholesterol, triglycerides
Thyroid function tests
Hepatitis screen (with tests for other blood-borne diseases, for example, HIV if indicated)
Anti-NMDAR, Anti-VGKC, Anti-GAD antibodies[a]
Urine drug screening
ECG
EEG (if indicated)
MRI scan of the brain[b]
Psychometric testing (if possible)[c]
Screening for sexually transmitted diseases (if indicated)

Source: Adapted from Freudenreich et al. (2009).
ESR: erythrocyte sedimentation rate; HIV: human immunodeficiency virus; NMDAR: *N*-methyl-D-aspartate receptor; VGKC: anti-voltage-gated potassium channel; GAD: glutamic acid decarboxylase; ECG: electrocardiogram; EEG: electroencephalogram; MRI: magnetic resonance imaging.
[a]Liaise with neurology colleagues on the interpretation of test results.
[b]Expert opinion is divided about whether MRI scan of the brain is necessary for all people with first-episode psychosis.
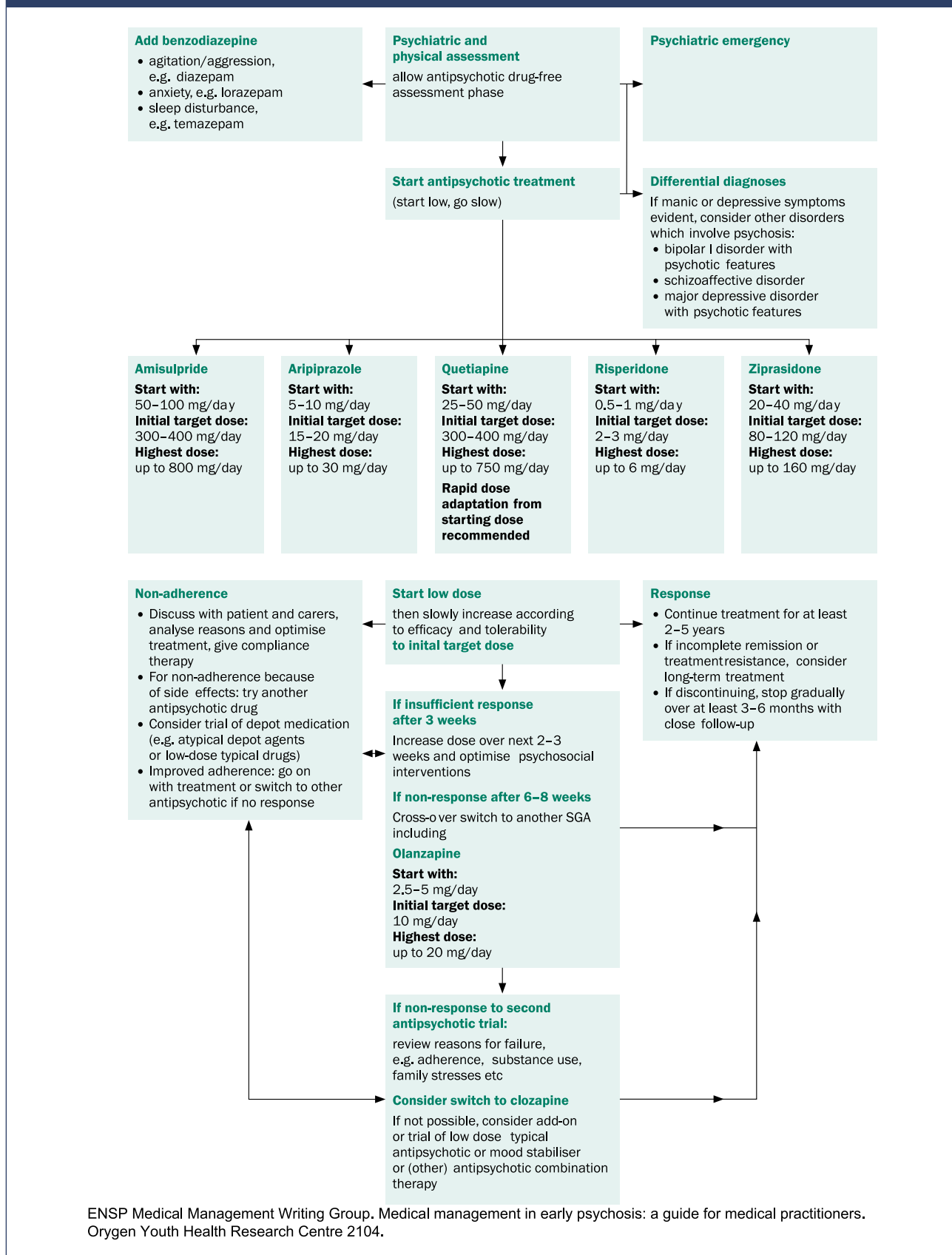[c]It may be necessary to wait until the mental state is stable before performing psychometric testing.

agents (FGAs) due to their better tolerability and extrapyramidal side-effect profile (Kahn et al., 2008) (see 'Antipsychotic medication' in 'Section 3. Treatment: context, structure and content of interventions'). There is some evidence of improved relapse prevention with SGAs, compared with FGAs, although this meta-analysis included only oral medications, and the most common FGA comparator was haloperidol (Kishimoto et al., 2013).

There are high levels of non-adherence to medication among people with psychotic disorders. Adherence should be proactively and sensitively addressed. There is a need for careful ongoing monitoring of medication in this stage of illness, combined with a willingness to decrease dosages. This is likely to work better in the presence of a multi-dimensional psychosocial programme to assist recovery.

Attempting to avoid relapse has been a rationale for medication in the management of FEP. Many researchers have emphasised the need for ongoing treatment to prevent relapse (Emsley et al., 2012) and the negative impact of relapse on the long-term course of the disorder (Emsley et al., 2013a). However, a recent study (Wunderink et al., 2013) observed that compared with a standard maintenance treatment regimen, dose reduction or supervised discontinuation of antipsychotic medication during the early phases of FEP led to a higher relapse rate initially, but improved long-term outcomes. This study has been criticised for its unequal distribution across diagnostic groups, high attrition rate, failure to separate the dose reduction and discontinuation groups, and the fact that most patients in each arm of the study did receive medication. These findings have not been replicated. See also

guide.medlive.cn

Figure 1. Pharmacological treatment for first-episode non-affective psychosis.

Add benzodiazepine
- agitation/aggression, e.g. diazepam
- anxiety, e.g. lorazepam
- sleep disturbance, e.g. temazepam

Psychiatric and physical assessment
allow antipsychotic drug-free assessment phase

Psychiatric emergency

Start antipsychotic treatment
(start low, go slow)

Differential diagnoses
If manic or depressive symptoms evident, consider other disorders which involve psychosis:
- bipolar I disorder with psychotic features
- schizoaffective disorder
- major depressive disorder with psychotic features

Amisulpride
Start with: 50–100 mg/day
Initial target dose: 300–400 mg/day
Highest dose: up to 800 mg/day

Aripiprazole
Start with: 5–10 mg/day
Initial target dose: 15–20 mg/day
Highest dose: up to 30 mg/day

Quetiapine
Start with: 25–50 mg/day
Initial target dose: 300–400 mg/day
Highest dose: up to 750 mg/day
Rapid dose adaptation from starting dose recommended

Risperidone
Start with: 0.5–1 mg/day
Initial target dose: 2–3 mg/day
Highest dose: up to 6 mg/day

Ziprasidone
Start with: 20–40 mg/day
Initial target dose: 80–120 mg/day
Highest dose: up to 160 mg/day

Non-adherence
- Discuss with patient and carers, analyse reasons and optimise treatment, give compliance therapy
- For non-adherence because of side effects: try another antipsychotic drug
- Consider trial of depot medication (e.g. atypical depot agents or low-dose typical drugs)
- Improved adherence: go on with treatment or switch to other antipsychotic if no response

Start low dose
then slowly increase according to efficacy and tolerability **to initial target dose**

Response
- Continue treatment for at least 2–5 years
- If incomplete remission or treatment resistance, consider long-term treatment
- If discontinuing, stop gradually over at least 3–6 months with close follow-up

If insufficient response after 3 weeks
Increase dose over next 2–3 weeks and optimise psychosocial interventions

If non-response after 6–8 weeks
Cross-over switch to another SGA including

Olanzapine
Start with: 2.5–5 mg/day
Initial target dose: 10 mg/day
Highest dose: up to 20 mg/day

If non-response to second antipsychotic trial:
review reasons for failure, e.g. adherence, substance use, family stresses etc

Consider switch to clozapine
If not possible, consider add-on or trial of low dose typical antipsychotic or mood stabiliser or (other) antipsychotic combination therapy

ENSP Medical Management Writing Group. Medical management in early psychosis: a guide for medical practitioners. Orygen Youth Health Research Centre 2104.

'*Antipsychotic medicines for FEP*' in '*Section 3. Interventions: context, structure and content*'.

Non-pharmacological approaches. For people with FEP, as for all people with psychotic illness, medication is only a part of the required treatment. Studies have shown that an early functional recovery is more predictive of a long-term full recovery than early symptomatic recovery alone (Álvarez-Jiménez et al., 2012a). This finding also aligns with the goals of young people with FEP. The top five goals, in order, are employment, education, housing, relationships and health (Iyer et al., 2011; Ramsay et al., 2011). Therefore, it is imperative to provide psychosocial interventions designed to achieve these goals.

Compared with standard treatment, comprehensive FEP services have demonstrated greater family satisfaction and lower family burden (Jeppesen et al., 2005). In addition, the provision of family psychoeducation and family group therapy can help reduce relapse and readmission rates (McNab and Linszen, 2009).

Unemployment is a significant area of disability for people with psychosis (Killackey et al., 2006). Education, the foundation of career, is often disrupted through the onset of illness (Waghorn et al., 2012). Working is one of the defining normative activities of adults in all societies. It is also the main avenue by which individuals achieve independence and social and economic inclusion. It therefore makes sense to start rehabilitative efforts in this area during the first episode. By doing this, a track record of employment is developed, training is completed and the skills associated with job seeking and working are acquired. Supported employment is the most successful of the vocational interventions (Drake et al., 2012), and individual placement and support is the most effective form of supported employment. Two RCTs of individual placement and support in people with FEP have demonstrated vocational recovery in over 80% of participants receiving this intervention (Killackey et al., 2008; Nuechterlein et al., 2008b). A number of other non-randomised trials of individual placement and support in young people with FEP have found that about two-thirds of participants return to school and/or work, and this effect persists for at least 2 years (Rinaldi et al., 2010). See also '*Vocational rehabilitation*' in '*Section 3. Treatment: context, structure and content of interventions*'.

Physical health should be addressed early in the course of illness (International Physical Health in Youth [iphYs] Working Group, 2013). Long-term physical health outcomes for people with schizophrenia and related disorders are poor (Galletly et al., 2012; Mitchell et al., 2013). Obesity and tobacco smoking are overwhelmingly responsible for the excess mortality (Olfson et al., 2015; Thornicroft, 2011). Weight gain due to side effects of medicines occurs disproportionately early in the course of illness, so monitoring and prevention at this point are obvious interventions (Foley et al., 2013). Monitoring needs to be systematic and regular, and monitoring protocols can assist in managing cardiometabolic health (Curtis et al., 2012; Stanley and Laugharne, 2014). However, no randomised trials assessing the effectiveness of physical health monitoring in people with serious mental illness have been completed (Tosh et al., 2014). There is some evidence that lifestyle interventions can prevent weight gain (Curtis et al., 2015; Daumit et al., 2013; Álvarez-Jiménez et al., 2006). Further research is needed, including replication of these studies and demonstration of enduring long-term benefit (Gates et al., 2015). Metformin has been found to limit weight gain in people with FEP (Jarskog et al., 2013). See also '*Section 4. Physical health*'.

There is currently no evidence to guide smoking cessation efforts in people with FEP. This is another area that requires further research. In the meantime, the recommendations of Mendelsohn et al. (2015) should be followed.

Recommendations on the management of first-episode psychosis (stage 2)	Type	Level of evidence
Health policy should include community campaigns to increase public awareness of the signs of first-episode psychosis, coupled with support for comprehensive first-episode psychosis services.	EBR	II
Health professionals and others involved in the care of young people (e.g. GPs, Aboriginal health workers, school counsellors) should be able to recognise signs of first-episode psychosis and should advise or arrange referral to appropriate psychiatric services as soon as possible.	CBR	N/A
The aim of psychiatric care for people with first-episode psychosis should be to provide effective treatment as soon as possible, so as to reduce the duration of untreated psychosis.	EBR	I
Comprehensive treatment should be provided continuously for 2–5 years.	EBR	II
Second-generation antipsychotic agents should be used in preference to first-generation antipsychotic agents.	CBR	N/A
Assess and discuss adherence continually. If non-adherence is identified, address it.	CBR	N/A
Provide family interventions.	EBR	I
Provide individual placement and support vocational recovery services.	EBR	I
Use lifestyle interventions to prevent weight gain.	EBR	II
Consider prescribing metformin to prevent weight gain for patients taking second-generation antipsychotic agents that are associated with risk of weight gain, when these risks cannot adequately be managed by switching medication or by lifestyle measures.	EBR	II

GP: general practitioner; EBR: evidence-based recommendation; CBR: consensus based recommendation.
N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

guide.medlive.cn

Further guidance on the assessment and management of early psychosis is provided in the Australian Clinical Guidelines for Early Psychosis: www.ranzcp.org/Publications/Guidelines-for-clinical-practice/Schizophrenia-early-psychosis-resources.aspx. The importance of holistic preventive health care in people with FEP is described in the Healthy Active Lives (HeAL) consensus statement 2013; available at www.nationalelfservice.net/cms/wp-content/uploads/2013/06/HeAL-international-concensus-statement.pdf. Information about managing cardiometabolic effects of antipsychotic medication in people with FEP is found in Positive Cardiometabolic Health: an early intervention framework for patients on psychotropic medication, NSW Government Health Education Training Institute (2011) (available at www.heti.nsw.gov.au/cmalgorithm).

Persistent/established illness (stages 3a, 3b, 3c). A significant proportion of people who have one episode of psychosis will go on to have more episodes or continuing disability. Naturalistic follow-up studies show that the early years after entry to treatment are often characterised by a turbulent early course, which can reduce ultimate levels of recovery (Birchwood and Fiorillo, 2000; Ho and Andreasen, 2001). Relapses are common, with about half of people with FEP relapsing during a 3-year follow-up period (Álvarez-Jiménez et al., 2012b; Robinson et al., 1999). Young people, in particular, find it difficult to accept the lifestyle change of taking medicines daily, especially if they have substantially recovered. Non-adherence to antipsychotic medication is a major risk factor for relapse during this period (Emsley et al., 2013b).

Relapses are disruptive and may contribute to an increased chance of treatment resistance. A substantial minority of people experience a 'stormy' early course of illness. Deaths from both suicide and natural causes occur at a much higher rate than in the general population (Power et al., 2003; Yuen et al., 2014). Secondary consequences such as persisting and worsening substance use and dependence, vocational failure, family stress and relationship breakdown are common. There is a serious risk of marginal lifestyles, homelessness and committing minor criminal offences. It is essential that high-quality, intensive care is continuously and assertively provided during this period. Recovery from an acute relapse can take longer than after the initial episode.

For some people, the move from specialised first-episode services to standard care results in loss of many of the gains made. This indicates the need for generic mental health services to provide the same level of support and assertive, individualised treatment as specialised FEP services. See also '*Section 3. Treatment: context, structure and content of interventions*'.

Management of acute relapse. It is important to determine the reason for relapse, carefully assessing adherence to medication and recent stressors. A family assessment can be helpful. Good adherence to antipsychotic medication and specific psychosocial interventions, particularly family interventions, may reduce the risk of relapse (Pharoah et al., 2010; Pilling et al., 2002; Schooler, 2005).

Poorly engaged individuals and those with frequent relapses benefit most from intensive case management (ICM) or assertive community treatment models of care (Marshall and Lockwood, 2011). All services should provide care based on this model of clinical intervention.

Comorbid substance use is another common contributing factor to relapse. A number of interventions, including CBT and motivational interviewing, have been developed to help people with severe mental illness manage substance abuse, but a recent Cochrane review (Hunt et al., 2013) found no evidence to support any one psychosocial treatment over another in terms of treatment engagement, reduction in substance abuse or improvement in mental state. See also '*Section 2. Comorbid substance use*'.

Key consideration
Family, personal and social support, a safe environment and an adequate standard of living are critical for people with an acute relapse of psychosis, because they are at risk of being marginalised and demoralised.

Recommendations on the management of acute relapse	Type	Level of evidence
Adequate sequential trials (at least 6 weeks of 300–1000 mg in chlorpromazine equivalents) of two antipsychotic medications, of which at least one should be a second-generation antipsychotic agent, should have been conducted. If these trials are unsuccessful, and adherence is known to be good, then clozapine should be considered.	EBR	I
If there has been poor or uncertain adherence, or it is the individual's preference, long-acting injectable antipsychotic medication should be considered.	EBR	I
CBT directed at persistent symptoms of psychosis should be offered. If CBT is unsuccessful, every effort should be made to persuade the individual and family to have a trial of treatment with clozapine. CBT should always be provided should there be no response to clozapine and vice versa.	EBR	I

guide.medlive.cn

Recommendations on the management of acute relapse	Type	Level of evidence
Poor adherence with treatment plans, side effects (including obesity and metabolic syndrome), depression, substance use, complications of polypharmacy and the quality of the social environment should be considered and addressed.	EBR	II
If positive symptoms persist despite an adequate trial of clozapine, consider either of the following treatment options: • Continue clozapine and prescribe adjunctive medication • Reinstate the previous regimen that was most effective and well tolerated and prescribe adjunctive medication	EBR	II
Treatment should include a focus on developing illness self-management skills.	CBR	N/A
Cognitive remediation should be offered when cognitive deficits are affecting recovery and function.	EBR	I
If deficits in social cognition are impeding an individual's social function, offer therapies to address these deficits.	EBR	I

CBT: cognitive behaviour therapy; CBR: consensus-based recommendation; EBR: evidence-based recommendation.
N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

Severe persistent or unremitted illness (stage 4). Clinical remission in schizophrenia is not uncommon, based on the findings of studies that have applied objective criteria (Andreasen et al., 2005). However, a substantial minority of people with schizophrenia have persisting disabling and distressing symptoms. Apparent treatment resistance should be a trigger to reassess the treatment plan. For information on the management of treatment-resistant schizophrenia, see '*Treatment resistance and clozapine*' in '*Section 3. Treatment: context, structure and content of interventions*'.

The recovery paradigm has reframed concepts of outcomes to include the subjective views of the person living with schizophrenia (Leamy et al., 2011; Slade, 2013). The therapeutic approach at this stage is guided by a person-centred value system of a 'life worth living'. More information about recovery is provided in '*The recovery paradigm*' in '*Section 3. Treatment: context, structure and content of interventions*'.

The clinician's role is to establish a mutually respectful therapeutic relationship and optimise the management of potentially treatable factors such as unrecognised depression, inadequate psychosocial rehabilitation, poor adherence to prescribed medicines, substance use, medication side effects, differential responses to medicines, drug interactions and suboptimal drug therapy. The clinician also needs to work in partnership with primary care physicians and NGOs to ensure physical health and non-clinical needs are adequately addressed.

Key considerations
Secure, safe housing and income support are key priorities for people with severe persistent illness.
Suboptimal care for patients with severe persistent or unremitting illness increases their risk of developing physical illness, social isolation and marginalisation.

Recommendations on the management of severe persistent or unremitted illness (stage 4)	Type	Level of evidence
A second opinion should be sought for people whose symptoms have responded poorly to treatment.	CBR	N/A
A recovery plan should be negotiated and agreed upon with the individual and reviewed regularly.	CBR	N/A
Psychosocial interventions should be provided.	CBR	N/A
The treatment plan should be concordant with the recovery model. It should be reviewed regularly to identify modifiable illness or lifestyle risk factors such as non-adherence or substance use.	CBR	N/A
Encourage people with schizophrenia to see their GP regularly. Mental health service clinicians should communicate with each patient's GP at least once every 6 months.	CBR	N/A
Mental health services should develop partnerships with non-governmental organisations that can assist in providing lifestyle support and encouraging social inclusion for people with schizophrenia.	CBR	N/A
Clozapine is the treatment of choice for people with treatment-resistant schizophrenia. When treatment resistance has been clearly demonstrated, clozapine should be offered within 6–12 months.	EBR	I
Optimal, comprehensive evidenced-based biopsychosocial care should be made available to all people with severe, unremitted psychotic illness.	CBR	N/A

CBR: consensus-based recommendation; GP: general practitioner; EBR: evidence-based recommendation.
N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

Section 2. Comorbid substance use

Psychosis and substance use

Comorbid substance use is a major complication of schizophrenia and an impediment to effective treatment and recovery. In the 2010 Australian National Survey of Psychotic Disorders, a diagnosis of harmful use of, or dependence on, psychoactive substances was made in 63.2% of men and 41.7% of women with psychosis (compared with 12.0% of men and 5.8% of women in the general population) (Moore et al., 2012).

Cannabis. Among people with psychosis, those with heavy cannabis use have a poorer prognosis. In addition, a systematic review of published data on cannabis exposure and the onset of schizophrenia (Large et al., 2011a) found that the use of cannabis brought forward the onset of schizophrenia by nearly 3 years. The increased risk appears to be dose-related and may be greater in those with a family history of schizophrenia.

Cannabis is arguably the most serious comorbidity with schizophrenia because of its widespread use among young people with mental illness (Schimmelmann et al., 2012). Cannabis use has a well-recognised role in triggering onset and exacerbations of schizophrenia (Gururajan et al., 2012; Stefanis et al., 2014) and is associated with a worse outcome and reduced efficacy of treatment (Gupta et al., 2013). Cannabis use can precipitate psychotic relapse in people with schizophrenia who had previously achieved remission.

Stimulants. Stimulants such as methamphetamine and cocaine can trigger psychotic states in people with schizophrenia and tend to exacerbate acute psychotic symptoms. Reported rates of stimulant use disorder in people with psychosis are much higher than in the general population (Sara et al., 2015). However, amphetamine use does not seem to have a measurable effect on the incidence of schizophrenia (Sara et al., 2015). People with schizophrenia are particularly sensitive to the psychotogenic effects of stimulant drugs, which act by releasing dopamine (Seeman and Seeman, 2014). This effect is evident in those experiencing FEP who have never been treated with antipsychotic medication and in those who have received treatment. Moreover, there appears to be a dose-related effect, with more frequent transient psychotic states and longer episodes of psychosis in more frequent and heavier users (McKetin et al., 2013).

Alcohol. Alcohol use disorders (AUD) are common in schizophrenia, with one Australian study finding as many as 57% of inpatients and 46% of outpatients meeting the criteria for the diagnosis of an AUD (Dawe et al., 2000). The prevalence of comorbid lifetime AUD worldwide is 20.6% (Koskinen et al., 2009). Alcohol abuse contributes to violence, imprisonment and homelessness of people with schizophrenia and is also associated with a worse outcome through non-adherence to treatment and poor physical health. Despite these problems, there has been relatively little research on the effects of alcohol in people with schizophrenia.

Managing substance use

There is often a separation between drug and alcohol and mental health services, with variable levels of collaboration between the two services. Integration of mental health services and drug treatment services would make treatment for alcohol and other drugs more accessible to people with psychotic illness, and this approach may be more effective (Brunette and Mueser, 2006).

CBT strategies have been used in the management of substance use in people with psychotic illness (Lubman et al., 2010). These approaches aim to examine the motivations for substance use, especially lifestyle factors, and teach more effective interpersonal and coping skills. Engaging the social network can also be helpful in managing substance use (Mueser and Gingerich, 2013).

Despite the lack of robust empirical evidence for the efficacy of these interventions (Hunt et al., 2013), motivational interviewing and integrated therapy (which combines CBT with lifestyle interventions and case management) are recommended approaches to the management of comorbid substance use in schizophrenia. An encouraging observation is that a high proportion of people do give up substance use after the first episode of illness (Wisdom et al., 2011).

Recommendations on comorbid substance use, including alcohol use disorder	Type	Level of evidence
Assertive treatment of comorbid substance use should be part of every treatment plan.	CBR	N/A
Motivational interviewing, integrated CBT and anti-craving or replacement medication are recommended interventions for comorbid substance use.	CBR	N/A
For individuals whose substance use is persistent and harmful, consider involuntary admission to hospital and/or referral to a long-term rehabilitation service.	CBR	N/A
The prescription of stimulant drugs for attention deficit hyperactivity disorder in people who have had an episode of psychosis or are at high risk of developing psychosis is not recommended.	CBR	N/A

CBR: consensus-based recommendation; CBT: cognitive behaviour therapy.
N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

guide.medlive.cn

Drug-precipitated psychosis

Only a small proportion of people who use cannabis, stimulant drugs or hallucinogens become psychotic. Therefore, any person presenting with delusional beliefs apparently emerging as a result of having used one of those drugs should be considered, at a minimum, to be at ultra-high risk of developing psychotic illness.

It can be difficult to separate drug-induced psychotic states from relapsing mental illness. However, drug-precipitated psychoses, including the toxic delirium that follows persistent amphetamine use, are typically transient, and present with illusions rather than true hallucinations,

plausible persecutory beliefs, affect that is appropriate to the content of the beliefs and an absence of thought disorder. People with symptoms that are persistent rather than transient or with auditory hallucinations, bizarre and enduring delusional beliefs, incongruous or blunted affect or thought disorder should be suspected of having a primary psychotic illness requiring longer term observation and treatment.

A significant proportion of people admitted to hospital with a diagnosis of drug-precipitated psychosis go on to develop chronic and relapsing psychotic illness (Crebbin et al., 2009; Sara et al., 2014). Therefore, close monitoring

Recommendations on drug-precipitated psychosis	Type	Level of evidence
The emergence of delusional beliefs associated with drug use should be considered as an ultra-high risk state for developing schizophrenia or a related psychotic illness.	CBR	N/A
Wherever possible, the presence of a drug should be established at the time of contact with mental health services, with either urine or saliva drug testing.	CBR	N/A
Outpatient review or referral to an early psychosis service is recommended.	CBR	N/A
Antipsychotic medication should be withdrawn only under medical supervision.	CBR	N/A
Counselling regarding drug use and referral to a specialist drug counselling or dual diagnosis service is recommended.	CBR	N/A
Recurrent episodes of psychosis occurring despite treatment with an adequate dose of antipsychotic medication should raise the suspicion of use of stimulant drugs or cannabis.	CBR	N/A

CBR: consensus-based recommendation.
N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

of such individuals (with drug-free periods, if possible) is important, as is counselling about the harms of drug use.

Section 3. Treatment: context, structure and content of interventions

The recovery paradigm

Recovery-oriented practice is based on the central importance of the lived experience and the perspective of the person with mental illness. Distinctions can be made between clinical recovery (which includes lessening of symptoms), functional recovery and personal recovery (Slade, 2009). Personal recovery has been described as a unique process of changing one's attitudes, values, feelings, goals, skills and/or roles (Anthony, 1993). It is a way of living a satisfying, hopeful and contributing life even within the limitations caused by illness. The concept of personal recovery draws on constructs of hope, self-identity, meaning and personal responsibility (Slade, 2009). For the individual, gaining knowledge about the disorder and the available treatment options, developing illness self-management skills and taking responsibility for his or her own treatment are all important.

Recovery-oriented services emphasise peer relationships, social networks, person-centred (strengths-based) assessment and recovery planning. People are encouraged to take up new challenges. Risk can be reduced through the use of relapse prevention plans and advanced health directives, along with the development of self-management skills to prevent unnecessary crises and minimise the loss of personal responsibility during periods of crisis.

Recovery is a concept relevant to all stages of illness, beginning as soon as there is a need for care (in the prodromal or ultra-high risk period) and continuing through the first episode and the critical period. Recovery is a key goal in real terms and not merely in the sense of acceptance of persistent illness or adapting around it to have a meaningful life (critical though this is for many people). Clinicians should aim for recovery for everyone, and across all stages, as there are often late remissions or improvements.

Interventions essential to community-supported recovery include supporting people in early prodromal or symptomatic stages, responding quickly to requests for assistance, providing meaningful support, planning together with individuals and carers, listening to family members, facilitating connections with peer support networks and

guide.medlive.cn

professional advocates, ready access to suitable facilities and helping people stay in their own accommodation (Mental Health Council of Australia [MHCA], 2006). Assistance needs to be personalised to the individual. An essential component of care is coordination of complex systems and assistance in negotiating the common barriers of social and economic disadvantage.

Training for clinicians should include both the values and the practical aspects of the recovery model. The required recovery competencies include an awareness of recovery within a cultural context, understanding and accommodating diverse views on mental illness and treatment, respectful communication, appreciating the individual's resourcefulness and understanding the impact of stigma and social exclusion (Mental Health Commission, 2001).

In Australia, the national framework for recovery-oriented mental health services (Australian Health Ministers' Advisory Council, 2013) recommends provision of a respectful environment which allows people to be treated with dignity, and the implementation of recovery principles across multiple levels of service delivery. Standardised instruments have been

Key consideration
The recovery approach is the guiding principal of contemporary mental health services and should be incorporated into all aspects of service delivery.

Recommendations on recovery-oriented practice	Type	Level of evidence
Recovery training should be mandatory for all clinicians working in mental health.	EBR	III-3
People with mental illness should be treated in an appropriate, caring and respectful environment that promotes a collaborative relationship between the individual and clinicians.	CBR	N/A
A recovery plan developed in partnership with the person with mental illness should guide mental health care.	EBR	I
Psychoeducation should be available.	EBR	I
Peer specialists should be employed to assist with counselling, support and psychoeducation for people with schizophrenia, provide advice to clinicians and help plan and audit services.	EBR	III-2
Clinicians and mental health services should work in partnership with the individual, their carers, the non-government sector and relevant support organisations.	EBR	I

CBR: consensus-based recommendation; EBR: evidence-based recommendation.
N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

developed to measure individual recovery (Shanks et al., 2013) and the recovery-orientation of services (Williams et al., 2012), which should enable more research and evaluation.

The service system and models of intervention

Mental health care in Australia and New Zealand is centred on community-based care in both public and private sectors. Reliance on inpatient beds has been decreasing over recent years (Raudino et al., 2014). The National Mental Health plans of both countries (Australian Government Department of Health, 2009; New Zealand Ministry of Health, 2012) emphasise partnerships between mental health services, primary care providers, private providers, the non-government sector, peer operated services and family-based care.

For many, the GP is well positioned to coordinate care and attend to the physical health needs of people with mental illness. Cost and access barriers need to be acknowledged and addressed. Emerging methods of service delivery, such as telemedicine and online mental health education and therapies, may be especially helpful for people living in rural and remote communities.

Mental health services generally have the following elements:

- Inpatient services
  - acute beds
  - subacute 'step-up, step-down' beds
  - residential rehabilitation
  - extended care beds
  - consultation liaison services
  - psychiatric emergency care, usually attached to the emergency departments of hospitals

guide.medlive.cn

- Specialised ambulatory care mental health services
  - crisis teams or community assessment and treatment teams which provide acute phase community-based assessment, treatment and, where appropriate, home-based care
  - community mental health continuing care teams offering multidisciplinary extended mental health care in the community
  - developmentally specific teams including early intervention teams and aged care teams
  - assertive community treatment teams and intensive case management (ICM) providing mobile care to a more complex subset of people including both home-based treatment and hospital diversion
  - community-based clinical care in residential rehabilitation units
- Specialised mental health community support
  - individual and group peer support often related to lifestyle or education and employment
  - family and carer support
  - respite services
  - non-clinical residential services
- Private sector mental health providers
  - primary care physicians
  - psychiatrists
  - psychologists and other counsellors
  - community and day programmes
  - inpatient facilities.

The second Australian National Survey of Psychosis demonstrated the positive impact of some of the recent changes, which include increased community staffing and funding for services provided by the non-government sector (Neil et al., 2013). However, social and economic disadvantages remain significant challenges for people living with psychosis (Morgan et al., 2012).

Intensive case management (ICM). ICM is a model of service delivery for people with severe mental illness, most commonly schizophrenia. ICM has evolved from assertive community treatment, a model that relies on team-based management rather than individual caseloads. Both models include frequent service contact, mobile active outreach and low staff–patient ratios. Better outcomes are achieved by community services that have higher levels of fidelity to the ICM model.

A Cochrane review of RCTs (Dieterich et al., 2010) compared ICM (in which case managers had a caseload of fewer than 20 patients) with non-intensive case management (where patients had the same package of care but case managers had a caseload of more than 20 patients), and with standard care. Compared with standard care, people receiving ICM were significantly more likely to stay in contact with the service and had a lower rate of hospitalisation, a higher rate of stable

housing and better overall function. The only difference between ICM and non-intensive case management was that the ICM patients were more likely to remain engaged in care.

Non-government services. The Australian and New Zealand governments are making significant investments in the non-government sector. NGOs provide a diverse range of services to the mentally ill and are considered to be more flexible, responsive and innovative than public mental health services.

NGO services provide a range of housing options, including staffed residential facilities for people who require help with illness stabilisation, skill retrieval and development, and community integration over a longer period of time. People with schizophrenia who have disabling cognitive or negative symptoms can benefit from community support worker interventions. These can range from low-level support, such as a face-to-face contact once a week, to higher frequency support delivered after a comprehensive needs assessment in the form of a 'package of care'. Packages of care can consist of both individualised hours of face-to-face support and assistance with the person's physical environment and organising their daily activities. Finding the most suitable services and coordination of care can be difficult especially when there are numerous small NGOs, and improved links between NGO-based community care services and clinical services are needed. Innovative models exist where mental health and NGO clinicians are co-located and work as a virtual team providing integrated care for people with significant mental illness.

NGOs also provide specific services to people from diverse cultural groups such as Australian Aboriginal and Torres Strait Islander people, Māori, Pacific Peoples and refugees. For those who have had adverse experiences with clinical services or difficulty trusting clinicians, involvement with the NGO sector can be an effective way of engaging with treatment.

Primary care. There are several models for working with GPs. It is preferable that people with schizophrenia who have significant ongoing symptoms and disability and a history of serious severe psychotic relapses are followed up by specialist mental health services. These individuals will benefit from the input of a multidisciplinary team and regular assertive follow-up to ensure continuity of treatment. The GP may play an important role in managing physical health conditions. GPs should receive appropriate clinical information, including the treatment plan, and should have regular communication with mental health clinicians.

Sometimes people with schizophrenia who have had a period of stability under specialist mental health services are considered suitable to have further mental health care transferred to general practice. Before this happens, the following issues should be considered:

guide.medlive.cn

- The individual and their family, carers and/or support people need to have participated in the development of a relapse recovery plan.
- There should be a clear, shared understanding of the role of medication in relapse prevention and how medicines will be prescribed, dispensed and monitored.
- There should be careful consideration of which GP would be providing the follow-up and how the

person would access this service. Before a transfer to primary care, it is appropriate for specialist mental health to contact the primary care practice to discuss the follow-up needs of the individual and to provide clear written information regarding the treatment plan.

Rural and remote services. In rural and remote regions of Australia and New Zealand, resources for the care of people with

Key consideration
People with schizophrenia should have access to specialist continuing care teams, working in partnership with general practitioners and other care providers. Continuing care teams and case management are a key component of long-term care.

Recommendations on service provision	Type	Level of evidence
Assertive community treatment should be offered after initial contact, during crises and after discharge from hospital.	EBR	I
Service models should include clearly established pathways for transition of patients between services, especially between mental health services (e.g. child and youth services to adult services) and external partners (mental health services to GPs, private psychiatrists, non-governmental organisations).	CBR	N/A
People with schizophrenia should be strongly encouraged to see a GP for preventative health care and treatment of physical conditions.	CBR	N/A
Mental health services and private psychiatrists must have the ability to monitor physical health and arrange appropriate treatments, particularly for people who refuse to see GPs.	CBR	N/A
Mental health services should develop clear guidelines for clinical communication and shared responsibility between GPs, private psychiatrists and non-governmental organisations.	CBR	N/A

EBR: evidence-based recommendation; CBR: consensus-based recommendation; GP: general practitioner.
N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

mental illness are scarce, as for many areas of medicine. The number of psychiatrists per population is less than in urban regions, and distances from hospitals are greater.

In these settings, it may be the GP who will be the main medical contact for people with schizophrenia rather than a psychiatrist. If possible, psychiatric opinions should be sought especially when there is diagnostic uncertainty or complexity such as dual diagnosis or treatment resistance. Telemedicine services can be useful in enabling ongoing specialist assessment and advice.

Antipsychotic medication

Overview. Antipsychotic medicines treat the symptoms of schizophrenia but not its underlying causes. In the absence of new treatments, these medicines remain the cornerstone of both acute and maintenance therapy for schizophrenia. All antipsychotic medicines derive their effect on positive symptoms of psychosis from the blocking of dopamine receptors. These medications are described as FGA or SGA, but this distinction is not a neat one and the

individual properties of each agent should be taken into account. The reason for including the distinction in this guideline is that much of the quoted literature uses the distinction. It can be expected that the classification into FGA/SGA will become less recognised in clinical practice over time.

Most FGAs are high-potency medicines that are tightly bound to dopamine receptors and often cause debilitating extrapyramidal side effects (see Table 6 for the approximate relative frequency of common side effects of individual antipsychotic drugs). There is little evidence that the SGAs are more effective than the FGAs in the acute treatment of positive symptoms. However, there is some evidence that oral SGAs are more effective than oral FGAs in relapse prevention (Kishimoto et al., 2013). Furthermore, there are data suggesting that some of the SGAs are more effective for managing negative and neurocognitive symptoms (Zhang et al., 2013a).

However, some of the SGAs have serious adverse effects, especially metabolic and cardiac side effects. Metabolic changes have been detected even in the young (Foley et al.,

2013), so monitoring and intervention should begin early for people prescribed these medicines. Where possible, medicines with the least risk of weight gain should be selected (Bak et al., 2014). Extrapyramidal side effects, akathisia and tardive dyskinesia can occur with both FGAs and SGAs, although in general these tend to be more common with FGAs.

Neuroleptic malignant syndrome (NMS) is a rare and potentially life-threatening condition characterised by fever, rigidity, tremor, sympathetic nervous system dysregulation and creatine kinase (CK) elevation (Tse et al., 2015). Prompt diagnosis and treatment (usually in a general hospital) are essential. Both FGA and SGA can cause NMS. More information about side effects is available in *'Management of antipsychotic side effects'* in this section.

Antipsychotic medicines are associated with substantial inter-individual variation in both efficacy and adverse effect profiles. It is essential that clinicians work with the individual to find the best possible medication for them in terms of both efficacy and tolerability, and develop a dosing regimen that will minimise the impact of side effects on daily function. The proposed choice of antipsychotic medicine should be discussed with the person who will be taking it, providing information about both expected benefit and side effects. Their previous experiences with medication should be taken into account.

There may be differences in tolerability between ethnic groups. For example, East Asian people may require lower doses and be more sensitive to extrapyramidal side effects (Ormerod et al., 2008). Clinicians prescribing anticholinergic agents should be aware of contraindications to these medicines and advise about possible anticholinergic side effects.

Aids to medication adherence such as dose administration aids, packed by the dispensing pharmacist or by the individual or carer, and programmed reminders (e.g. on a mobile phone) can be useful. Long-acting injectable (also known as depot) antipsychotic agents can be helpful if adherence is poor or uncertain (Bosanac and Castle, 2015); sometimes there is an impression of good adherence when in fact little medication is being taken. Depot medications bypass hepatic first-pass metabolism.

Key consideration
Early management of schizophrenia requires a multidisciplinary team approach, including appropriate psychopharmacological interventions and comprehensive psychosocial supports.

Recommendations on medication in first-episode psychosis	Type	Level of evidence
The management plan should be discussed fully with the individual and their family/carers, wherever possible. The benefits and risks of drug therapy should be explained in a non-coercive manner.	EBR	II
Medication should be used in combination with psychosocial interventions, including strategies to encourage adherence to medicines.	EBR	II
The choice of antipsychotic medicines should be based on: • the individual's preference after risks and potential benefits have been explained, • the person's prior response to the medicine (if known), • clinical response to an adequate treatment trial, • individual tolerability, • potential long-term adverse effects.	EBR	I
The lowest effective antipsychotic dose should be used to establish treatment acceptance and minimise side effects.	EBR	II
Prescribe only one antipsychotic agent at a time, unless it has been clearly demonstrated that the person's symptoms are resistant to monotherapy.	EBR	II
Prescribe antipsychotic medicines at doses that are adequate to prevent relapse, suppress symptoms and optimise the person's subjective wellbeing.	EBR	II
Provide an adequate duration of treatment. Monitor treatment and adverse effects appropriately.	EBR	II
Consider the use of long-acting injectable antipsychotic medicines if: • the individual prefers a long-acting injectable medicine, • adherence has been poor or uncertain, • there has been a poor response to oral medication.	EBR	II
Treatment with clozapine should be considered early if appropriate pharmacological interventions are ineffective.	EBR	I

EBR: evidence-based recommendation.

guide.medlive.cn

Antipsychotic medicines for FEP. A treatment algorithm for *pharmacological treatment for first-episode non-affective psychosis* is provided in Figure 1 (above).

Oral SGAs should be prescribed as first- and second-line treatment for people with FEP. The choice of SGA depends on various factors such as side effects, tolerability/ discontinuation rate and long-term outcomes. The initial dose should be low. If response is slow or incomplete, the dose should be increased slowly at suitable intervals.

Distress, insomnia and agitation can be treated initially with benzodiazepines. Other symptoms such as mood elevation and depression require specific treatment with mood stabilisers and antidepressants.

Antipsychotic medicines for acute relapse and maintenance therapy (stages 3a, 3b, 3c)

Acute phase. Where possible, the choice of antipsychotic medicine should take into consideration prior response to treatment, side effects and the person's preference. Oral SGAs are usually the treatment of choice, in view of their generally lower risk of extrapyramidal side effects, compared with FGAs.

Long-acting injectable antipsychotic agents, particularly SGAs, provide an important treatment option in all phases of the disease for people whose adherence to oral treatment is poor. For some patients, the use of long-acting injections is a convenient option to overcome the need of taking medications every day and maintain remission. Thus, an appropriate and non-judgemental approach should be part of the pharmacological discussion. If it is clear that a long-acting injectable antipsychotic is the most suitable choice for maintenance therapy, selection of the appropriate oral antipsychotic that is available as a long-acting injectable will provide an option for later change (e.g. initiation of zuclopenthixol hydrochloride tablet prior to administration of zuclopenthixol decanoate long-acting injectable).

Parenteral administration of antipsychotics (along with benzodiazepines) may be required for the treatment of agitation in emergency situations when the person refuses oral medications (see '*The management of acute behavioural disturbance in schizophrenia and related disorders*' in this section).

Maintenance phase. In established illness, it is generally considered advisable to continue maintenance treatment with the prescribed antipsychotic to which the person responded in the acute episode, as long as the efficacy and benefits outweigh the side effects. However, if the drug is causing adverse effects such as weight gain, then switching to a drug with less potential for causing these side effects should be considered (see '*Switching medications*' in this section). If dose reduction is indicated, it should be performed gradually to avoid withdrawal effects and rebound psychoses. When planning long-term treatment, antipsychotic agents with the best balance between efficacy, side

effects and adherence for the individual should be selected. Higher doses than those usually recommended (Table 4) may sometimes be required, but there is a lack of research about efficacy and safety. Higher doses should be used cautiously, and careful monitoring of safety and tolerability is essential. Clozapine should be considered when there is a poor response or significant side effects.

If there are problems with adherence, the person's reasons for non-adherence and strategies to address these should be explored. A long-acting injectable antipsychotic agent should be considered, and this option should be discussed with the person and their carers.

Monitoring and treatment of side effects. During both the acute and maintenance phases of treatment, it is essential to regularly monitor antipsychotic adverse effects, including extrapyramidal side effects, akathisia, weight gain, cardiovascular and metabolic side effects (Curtis et al., 2012; De Hert et al., 2011) and tardive dyskinesia. Severe medication side effects, such as akathisia (Lohr et al., 2015), can be a risk factor for non-adherence, exacerbation of symptoms, aggression or suicide, and appropriate interventions should be undertaken promptly (see '*Management of antipsychotic side effects*', below). The management plan should include clear information about who is responsible for implementing physical health interventions (such as prescribing metformin, antihypertensive medication, organising dental care and/ or consultation with a dietitian). Information about managing cardiometabolic effects of antipsychotic medication in people with psychosis is found in Positive Cardiometabolic Health: an early intervention framework for patients on psychotropic medication, NSW Government Health Education Training Institute (2011) (available at www. heti.nsw.gov.au/cmalgorithm).

Cessation of medication. The decision to reduce, or possibly cease, medication requires careful discussion and evaluation of risks and benefits for each individual. The person should have made a full recovery and been well for at least 12 months before cessation of medication is considered. Severity of illness, risk factors, individual circumstances and family history should be taken into account, and medical supervision during and after medication cessation is essential. The support of family and friends, and their assistance in monitoring changes in mental state or social function, is helpful. An advance directive rescue plan, developed in collaboration with the person, their family and friends, can be very helpful if relapse does occur.

Long-acting injectable antipsychotic agents. Long-acting injectable antipsychotic agents provide an important option, particularly in the management of non-adherence, and can reduce relapse rates and rehospitalisation in people with FEP or schizophrenia (Kishimoto et al., 2013). They

Table 4. Dosing regimen for common oral antipsychotic agents.

Agent	Daily starting dose	Maximum recommended daily doses[a]
Amisulpride[b]	100 mg	1200 mg
Aripiprazole	10 mg	30 mg
Asenapine (sublingual tablet)[c]	10 mg (5 mg twice daily)	20 mg
Chlorpromazine[d]	75–100 mg	800 mg (TGA/TG-P)
Clozapine	12.5 mg	900 mg
Haloperidol[d]	0.5 mg (TGA/MNZ) or 1 mg (TP)	10 mg[e]
Lurasidone	40 mg	160 mg
Olanzapine	5 mg	30 mg (TG-P) or 20 mg (TGA/MNZ)
Paliperidone (controlled-release)	3 mg	12 mg
Pericyazine[d]	10 mg	300 mg (MNZ) or 75 mg (TGA/TG-P)
Quetiapine	50 mg	800 mg
Risperidone	0.5–1 mg	6 mg
Trifluoperazine[d]	2 mg	15–20 mg[e]
Ziprasidone[b,f]	80 mg (40 mg twice daily)	160 (80 mg twice daily)
Zuclopenthixol hydrochloride	10–20 mg	75 mg

Source: Adapted from product information approved by Australian Therapeutic Goods Administration, product information approved by Medsafe (the New Zealand Medicines and Medical Devices Safety Authority) and *Therapeutic Guidelines – Psychotropic* version 7 (Psychotropic Writing Group, 2013).
TGA: product information approved by Therapeutic Goods Administration, Australia; MNZ: product information approved by Medsafe, New Zealand; TG-P: Therapeutic Guidelines – Psychotropic version 7 (Psychotropic Writing Group, 2013).
[a]These doses may not be tolerated by some people.
[b]A lower dose is recommended for people with renal impairment.
[c]No food or drink for 10 minutes post dose.
[d]First-generation antipsychotic agent.
[e]Higher doses are approved for use but are not generally recommended due to risk of extrapyramidal side effects.
[f]Must be taken with food.

Table 5. Long-acting injectable antipsychotic agents.

Agent	Usual dose range	Usual interval between injections	Notes
Aripiprazole	300–400 mg	4 weeks	Supplement with oral antipsychotic for 2 weeks during initiation.
Flupenthixol[a]	20–40 mg	2–4 weeks	Give second dose after 4–10 days then space out to every 2–4 weeks. Higher doses (up to 100 mg) have been used for treatment resistance.
Fluphenazine[a]	12.5–100 mg	2–4 weeks	An oral dose of 20 mg of fluphenazine hydrochloride is equivalent to fluphenazine decanoate 25 mg (1 ml) every 3 weeks.
Haloperidol[a]	25–200 mg	4 weeks	Initiate at a lower dose (maximum 100 mg) and adjust the dose upward as required. There is limited clinical experience with doses greater than 300 mg per month.
Olanzapine	300–400 mg	2–4 weeks	Post-injection delirium/sedation syndrome can occur in about 1% of recipients, so appropriate monitoring is required.
Paliperidone	25–150 mg	4 weeks	Loading dose can be given. Formulation with a duration of action of 3 months may become available soon.
Risperidone	25–50 mg	2 weeks	Supplement with oral antipsychotic for at least 3 weeks during initiation.
Zuclopenthixol[a]	200–400 mg	2–4 weeks	Short-acting form (zuclopenthixol acetate) lasting 2–3 days is also available as second-line treatment of acute behavioural disturbance in schizophrenia.

[a]First-generation antipsychotic agent.

guide.medlive.cn

should only be prescribed when this is the person's preference or as part of a treatment plan in which adherence is a clinical priority.

Long-acting injectable antipsychotic agents can reduce the risk of accidental or deliberate overdose in high-risk individuals. However, adjustment to optimal dose may not be as flexible as oral antipsychotics and prolonged distressing side effects after discontinuation may occur. With some long-acting injectable antipsychotic agents, it may take 2–4 months to achieve the desired steady-state plasma concentrations (Table 5).

The side effects are essentially the same as the oral preparations; most are likely to cause extrapyramidal side

Recommendations on long-acting injectable antipsychotic agents	Type	Level of evidence
Long-acting injectable antipsychotic agents should be offered to patients early in the clinical course of schizophrenia.	EBR	II
Long-acting injectable antipsychotic agents are recommended in the treatment of schizophrenia and first-episode psychosis: • when it is the individual's preference • as part of treatment plan where adherence has been poor or uncertain • as part of the treatment algorithm where there has been a poor response to oral medication	EBR	II
Long-acting injectable antipsychotic agents should be actively promoted when patients are non-adherent to oral antipsychotic medication.	EBR	III-I
Olanzapine long-acting injection should only be given if observation by a clinician for at least 2 hours after each injection is available.	EBR	IV

EBR: evidence-based recommendation.

effects, with the exception of long-acting injectable olanzapine, which is associated with weight gain.

While SGAs are generally preferred, there is limited choice and occasionally there is a better result with a first-generation long-acting injectable antipsychotic agent. Careful monitoring for extrapyramidal side effects and tardive dyskinesia is needed.

It is vital to ensure that intended switching is completed appropriately:

- For most antipsychotic agents, an initial oral test dose is required before starting the long-acting injectable preparation.
- For olanzapine and paliperidone, a loading dose is recommended when switching from oral preparations to long-acting injectable preparations, so an initial oral supplement may not be required.

Switching medications. A slow crossover titration is preferred and close monitoring of mental state, side effects and rebound phenomena is essential during switching (Knox and Stimmel, 2004). Potential adverse events during crossover include the following:

- Cholinergic rebound (flu-like symptoms with malaise, agitation, anxiety, insomnia, nausea and diarrhoea) can occur if switching from an agent that has a high affinity for the muscarinic M1 receptor to an agent with low M1 affinity (e.g. switching from clozapine to risperidone or aripiprazole). Slow crossover is advisable and short-term use of an anticholinergic such as benztropine is recommended.
- Rebound psychosis or extrapyramidal side effects – these are more likely to occur if switching from an agent that is loosely bound to the dopamine 2

Key consideration
Switching between antipsychotic agents should be achieved by planned slow crossover titration. The use of appropriate, short-term adjuvant therapies is recommended to minimise rebound phenomena.

Recommendations on switching between antipsychotic agents	Type	Level of evidence
If no response is achieved after 2–3 weeks despite treatment with an appropriate antipsychotic agent, given at the recommended dose and with good adherence, consider switching to another antipsychotic agent.	EBR	II
If treatment-related weight gain is a problem, consider adding metformin or switching to a weight-neutral antipsychotic agent.	EBR	II

医脉通
medlive.cn

guide.medlive.cn

receptor (D2), such as clozapine or quetiapine, and normally occur earlier than would be expected from a true psychotic relapse. Cross-titrate slowly and use symptomatic treatment such as a beta-blocker or benzodiazepine if necessary.

- Rebound insomnia – this may occur if changing from more sedating agents (clozapine, olanzapine) to less sedating agents (risperidone, paliperidone, amisulpride, aripiprazole). Give the new medication in the morning rather than the evening and prescribe a short-term hypnotic agent, such as temazepam or zopiclone, if needed.
- Unwanted pregnancy – this is more likely to occur when switching from antipsychotics that cause hyperprolactinaemia to antipsychotics with minimal prolactin elevation. It is important to educate women about this risk, and contraception should be considered.

Treatment resistance and clozapine

Definition. Treatment resistance is usually defined as continued positive symptoms after trials of at least two different antipsychotics at moderate doses (usually at least 300 mg chlorpromazine equivalents per day) for a reasonable period (usually at least 6 weeks). Every effort must be made to ensure the person has actually taken the prescribed medication, including a trial of a long-acting injectable agent in people suspected of non-adherence. It is important to differentiate non-response from lack of tolerability. There is a tendency to see resolution of positive symptoms as the main goal of treatment, but negative symptoms can be more disabling. It is important to differentiate primary negative symptoms from negative symptoms secondary to factors such as depression, anxiety or medication.

Clozapine. Clozapine can be a highly effective agent for those who fail to respond to other antipsychotic medications.

Ideally, treatment resistance should be identified early (within the first 6–12 months) and treatment with clozapine started without delay, to minimise the disability that develops with unremitting illness. Clozapine is the only antipsychotic shown to reduce suicidal behaviour in people with schizophrenia (Hennen and Baldessarini, 2005; Meltzer et al., 2003). The high side-effect burden means clozapine is reserved for people who have not responded to other treatments.

Mandated blood monitoring (weekly for the first 18 weeks, every 4 weeks thereafter) means that blood dyscrasia is likely to be detected, but cardiomyopathy and myocarditis are also potentially dangerous side effects. There is little evidence that the cardiac adverse events can be predicted, but baseline echocardiogram and troponin are advisable. Regular echocardiograms do not have a strong evidence base and it has been suggested that they be undertaken only if clinically indicated (Murch et al., 2013; Ronaldson et al., 2011). Metabolic monitoring and advice about diet and exercise are essential.

There is some evidence to support the use of metformin (500 mg bd) to minimise weight gain and insulin resistance for people taking clozapine (Chen et al., 2013). It is essential that the prescribing doctor is familiar with the unique profile of clozapine and can manage other less common side effects. If a person taking clozapine has a neutrophil count in the amber range, the addition of a low dose of lithium may be useful to protect against clozapine-induced neutropenia and maintain the person on clozapine (Paton and Esop, 2005).

It can take up to 12 months to see the full benefits of clozapine. If clozapine is ineffective, the choice is whether to augment clozapine with another drug or electroconvulsive therapy (ECT), or switch to another agent. If there has been absolutely no response and/or side effects are severe, a switch is suggested. Care needs to be taken in down-titration.

Recommendations on the use of clozapine in treatment resistance	Type	Level of evidence
Treatment-resistant disease should be recognised within 6–12 months of starting potentially effective antipsychotic treatment and confirmed as soon as possible.	EBR	II
A trial of clozapine should be considered for people with psychotic symptoms that are resistant to other antipsychotic agents. If possible, the trial should be continued for 12 months to allow for late responders.	EBR	I
Clozapine monitoring protocols should be followed rigorously.	EBR	III-1
Metabolic monitoring and interventions to manage the metabolic side effects of clozapine are essential.	EBR	II
Where clozapine monotherapy is ineffective, augmentation with other medicines or ECT can be considered.	EBR	III-1

EBR: evidence-based recommendation.

If clozapine has had some – even modest – benefit, augmentation is justifiable, although the evidence for this strategy is equivocal. On an individual level, the addition of a high affinity dopamine D2 blocking agent such as risperidone or amisulpride to clozapine can be effective for residual positive symptoms. The addition of aripiprazole to clozapine can effect significant weight reduction and improvement in metabolic parameters. Antidepressants and mood stabilisers cannot be recommended as adjuncts in the absence of mood or anxiety symptoms.

guide.medlive.cn

Recommendations on combining antipsychotic medicines	Type	Level of evidence
If an adequate response is not achieved after monotherapy treatment trials of two antipsychotic agents given separately at therapeutic doses, antipsychotic polypharmacy may be justifiable but requires careful monitoring.	EBR	II
If a patient is receiving two or more antipsychotic medicines, the medication regime should be regularly reviewed and simplified if possible.	EBR	III-3
The use of 'as-required' (prn) antipsychotic agents must be reviewed regularly to ensure that the total daily dose has not exceeded the maximum recommended dose.	EBR	III-1

EBR: evidence-based recommendation.

N-acetyl cysteine (Berk et al., 2008) and ethyl-eicosapentaoic acid (EPA) (fish oil) (Porcelli et al., 2012) are undergoing evaluation as clozapine augmenters. ECT has a limited place in the management of people with treatment-resistant schizophrenia (see '*Electroconvulsive therapy*' in this section), including those on clozapine (Petrides et al., 2015; Tharyan and Adams, 2005).

Combination of antipsychotic agents. The concurrent use of two or more antipsychotics for people with treatment-resistant or refractory schizophrenia is common practice, despite limited evidence to support this practice.

Compared with antipsychotic monotherapy, combined antipsychotic treatment has been associated with an increased side effect burden, high-dose prescribing, increased hospitalisation rates and length of stay, higher treatment costs and increased mortality (Gallego et al., 2012). Switching from polypharmacy back to monotherapy is possible, and strategies to reduce polypharmacy by educating clinicians to change their prescribing behaviour have had some success (Tani et al., 2013).

Recommendation on tobacco use with antipsychotic medications	Type	Level of evidence
People should be encouraged to reduce or cease tobacco smoking. If they are able to achieve this, then doses of antipsychotic medications may need to be adjusted.	EBR	III-3

EBR: evidence-based recommendation.

Smoking and antipsychotic medication. Smoking may increase the metabolism of particular antipsychotic agents (e.g. clozapine, olanzapine, haloperidol) via the induction of certain hepatic enzymes, particularly CYP 1A2. Plasma levels of both clozapine and olanzapine may be reduced by up to 50% in people who smoke tobacco products. If people taking these drugs cease smoking abruptly, the plasma levels can increase substantially and very rapidly.

Accordingly, higher doses of these antipsychotic agents are required to achieve the same therapeutic effect in smokers, compared with non-smokers (Taylor et al., 2015). It is therefore vital to routinely discuss smoking status and adjust the antipsychotic dosage appropriately. Clozapine levels should be closely monitored if there is a change in smoking behaviour, and the dose should be adjusted if necessary.

Nicotine replacement therapy, on the contrary, has no effect on this induction pathway. For information on strategies to support smoking cessation, see '*Smoking*' in '*Section 4. Physical health*'.

Management of antipsychotic side effects. Antipsychotic medications are associated with a range of side effects (Table 6) including neurological, metabolic, sexual, endocrine, sedative and cardiovascular side effects (Psychotropic Writing Group, 2013; Taylor et al., 2015). See also '*Section 3. Antipsychotic medication: overview*'. It is important to routinely assess people taking antipsychotic medications for side effects (Table 7) and consider appropriate intervention if necessary (Table 8) (Castle and Buckley, 2015; Lambert et al., 2010).

Australians with psychotic disorders have high rates of obesity and metabolic syndrome (Galletly et al., 2012). Several algorithms for screening and managing these problems have been developed in Australia (Curtis et al., 2012; Stanley and Laugharne, 2014). See also '*Metabolic syndrome and obesity*' in '*Section 4. Physical health*'.

If anticholinergic drugs are required to treat extrapyramidal side effects, their use should be reviewed after 3 months. It is sometimes possible to gradually withdraw the anticholinergics without changing the dose of the antipsychotic. Cessation of anticholinergics can be associated with improvement in cognition and in tardive dyskinesia (Desmarais et al., 2012).

Other classes of medicines commonly used in schizophrenia

Benzodiazepines. Benzodiazepines are commonly used for people with schizophrenia or related disorders, especially where there is a persistent high risk of aggression. While

Table 6. Approximate relative frequency of common side effects of antipsychotics.

Agent	Anticholinergic effects	Dyslipidaemia	Extrapyramidal side effects	Hyperglycaemia	Hyperprolactinaemia	Orthostatic hypotension	Sedation	Weight gain	QTc prolongation
Second-generation antipsychotic agents									
Amisulpride	−	?	+	−	+++	−	+	+	++
Aripiprazole	+	−	+	−	−	+	−	−[a]	−
Asenapine[b]	+	++	+	++	+	+	+	+	+
Clozapine	+++[c]	+++	−	+++	+/−	+++[d]	+++	+++	+
Lurasidone	−	−	+[e]	+/−	++[e]	−	−[f]	+/−	−
Olanzapine	++	+++	+/−	+++	+	+	++	+++	+
Paliperidone	+	++	+	+	+++	++[d]	+	++	+
Quetiapine	+	++	+	+++	+	++	++	++	++
Risperidone	+	++	+	++	+++	++[d]	+[d]	++	+
Sertindole	−	−	−	−	+	+[g]	−	+	+++
Ziprasidone	+	−	+	+	++	+	+	+	++
First-generation antipsychotic agents									
Chlorpromazine	+++	+++	++	+++	+++	+++[h]	+++	+++	++
Flupenthixol	++	?	++	++	+++	+	+	++	+
Fluphenazine	+	?	+++	++	+++	+	+	+++	+
Haloperidol	+	+	+++[i]	++	+++	+	+[h]	++	++
Pericyazine	+++	?	+	+[j]	+++	++	+++	++	?
Trifluoperazine	+	?	+++	+	+++	++	+	++	?
Zuclopenthixol	++[c]	?	++	+[j]	+++	+	+++	++	?

Sources: Table adapted with permission from Therapeutic Guidelines – Psychotropic version 7 (Psychotropic Writing Group, 2013); data on QTc prolongation from The Maudsley prescribing guidelines in psychiatry (Taylor et al., 2015); data on lurasidone from various sources (Australian Government Therapeutic Goods Administration, 2014; Citrome, 2013; Leucht et al., 2013; Peuskens et al., 2014).

?: Little or no information reported; −: Negligible or absent; +: Infrequent; ++: Moderately frequent; +++: Frequent.

The information in this table is based on a combination of reported adverse effect data and expert opinion; it is intended only as a guide and should be interpreted in the context of the person's particular situation (e.g. concurrent drugs, drug history, physical health, the considerable inter-individual variation in elimination half-lives) and doses.

aWeight loss reported.
bData on the frequencies of asenapine adverse effects are limited.
cHypersalivation reported.
dFrequency may be higher at the start of therapy or with rapid dose increase.
eAppears to be dose-related.
fSomnolence is a common observed dose-related adverse effect.
gHypersalivation reported.
hMore frequent with rapid dose increase.
iLower incidence with long-acting injectable formulation.
jReported to occur but no definitive data published as to the incidence.

guide.medlive.cn

Table 7. Monitoring for people taking antipsychotic medication.

	Baseline	4 weeks	8 weeks	12 weeks	24 weeks	Annually
Patient history	X					X
Weight (BMI)	X	X	X	X	X	X
Waist circumference	X			X	X	X
Fasting plasma glucose, HbA$_{1c}$	X			X	X	X
Fasting lipid profile	X			X	X	X
Prolactin	X	a	a	a	X	X
Full blood count	X				X	X
ECG	X				X	X
EEG	X					
Pregnancy test	X	a	a	a	a	a
Ophthalmological examination	X[b]					X[b]

Source: Adapted from De Hert et al. (2011).
BMI: body mass index; HbA$_{1c}$: glycated haemoglobin percentage; ECG: electrocardiogram; EEG: electroencephalograph.
[a]Monitor more frequently if clinically indicated.
[b]Particularly with quetiapine and chlorpromazine.

Table 8. Management strategies for side effects of antipsychotic drugs.

Effect	Strategies
Metabolic effects	
Obesity	Switch to an antipsychotic with low risk of weight gain
	Avoid polypharmacy if possible
	Provide appropriate advice about lifestyle interventions (diet and exercise)
	Consider metformin
Diabetes	Monitor serum glucose, treat with diet and hypoglycaemic drugs as indicated
	Monitor for complications of diabetes
Hypertension	Monitor BP, treat with antihypertensive if indicated
Elevated cholesterol and lipids	Switch to antipsychotic with low risk of elevating cholesterol and lipids
	Monitor lipid profile every 6–12 months
	Treat with statin drug if lifestyle interventions (diet and exercise) are insufficient
Neuromotor effects	
Acute dystonia (e.g. involuntary sustained spasm of muscles, oculogyric crisis)	Select antipsychotic with low incidence of extrapyramidal side effects
	Start with low dose and increase dose gradually
	Add anticholinergic agent (e.g. benztropine)
Chronic dystonia (e.g. sustained involuntary spasm of skeletal muscles)	Reduce dose or switch medication
Akathisia (e.g. feeling of 'inner restlessness', with a drive to move)	Reduce dose or select an antipsychotic with low risk for akathisia and increase dose slowly
	Add beta-blocker (e.g. propranolol), or a benzodiazepine or mirtazapine
Parkinsonism (e.g. mask-like facies, muscle rigidity, tremor, shuffling gait)	Reduce dose of antipsychotic drug
	Switch from FGA to SGA
	Administer oral anticholinergic agent
Tardive dyskinesia (e.g. orobuccofaciolingual movements)	Select an antipsychotic agent with low risk for tardive dyskinesia
	Evaluate risk factors for tardive dyskinesia
	Switch to clozapine or other SGA

(continued)

guide.medlive.cn

Table 8. (Continued)

Effect	Strategies
Anticholinergic effects	
Dry mouth	Reduce dose or select antipsychotic agent with lower risk
	Drink small amounts of fluid frequently
	Use other oral hygiene products for dry mouth
Excessive saliva	Administer sublingual atropine, oral hyoscine hydrobromide or oral benztropine
Constipation	Advise high-fibre dietary supplementation
	Increase physical activity, fluid intake
	Administer laxatives
Urinary incontinence	Reduce dose, if feasible
	Switch to another antipsychotic agent
	Management depends on the underlying aetiology
	Avoid high intake of fluids in the evening and ensure adequate voiding at bedtime
Cardiovascular effects	
Orthostatic hypotension	Titrate dose gradually
	Advise person to stand up slowly from sitting or lying position
	Decrease or divide doses of antipsychotic drug
	Switch to an antipsychotic without antiadrenergic effects
Tachycardia	Switch drug or add a low dose peripheral beta-blocker
QTc prolongation	Avoid combining drugs with a known risk for QTc prolongation
	If QTc > 450/470–500 ms or has increased more than 30–60 ms, switch to another antipsychotic
Hyperprolactinaemia	
Sexual dysfunction	Evaluation of prolactin level
	Exclusion of pituitary tumour
	Switch to a prolactin-sparing agent if there are symptoms of sexual and menstrual dysfunction. In women, discuss the risk of pregnancy and contraception.
Risk of osteoporosis	Bone density screening, switch drug if abnormal
Sedation	Titrate dose slowly
	Reduce dose (if applicable)
	Avoid concomitant use of other CNS depressants

Source: Adapted from Castle and Buckley (2015) and Lambert et al. (2010).
BP: blood pressure; FGA: first-generation antipsychotic agent; SGA: second-generation antipsychotic agent; CNS: central nervous system.

there is no good evidence for their use in the longer term (Dold et al., 2013), these agents can be useful in managing anxiety or brief exacerbations of symptoms.

Mood stabilisers. Mood stabilisers such as lithium and sodium valproate are commonly added to antipsychotic agents, especially in individuals who have an affective component to their illness, although there have been few methodologically sound RCTs evaluating the efficacy of these drugs in the management of schizophrenia (Leucht et al., 2007, 2014; Schwarz et al., 2008). Care needs to be taken with adding mood stabilisers, as an increase in mortality has been reported with antipsychotic–mood stabiliser combinations (Tenback et al., 2012).

Antidepressants. In the absence of comorbid depression, evidence for the use of antidepressants in people with psychotic illness is equivocal (Sommer et al., 2012) with limited evidence of benefit.

Omega-3 fatty acids. Fish oils contain EPA and docosahexanoic acid (DHA). Fish oil supplementation showed benefit for people with an at-risk mental state in a single study (Amminger et al., 2010), but this has yet to be replicated. An earlier Cochrane review (Irving et al., 2006) found that the evidence for using supplementary fish oil in people with schizophrenia was inconclusive.

Emerging treatments

It is important that clinicians independently review the evidence base for new treatments. New SGAs include lurasidone, which has recently become available, and iloperidone, which may be available soon. There are several promising emerging pharmacological approaches to the treatment of schizophrenia. A metabotropic glutamate receptor agonist showed efficacy for both positive and negative symptoms of schizophrenia (Marsman et al., 2013; Patil et al., 2007b), but these outcomes were not replicated and the agent has been withdrawn. Other glutamatergic agents are in various

guide.medlive.cn

stages of development, including the glycine transport inhibitors bitopertin and sarcosine (Arango et al., 2013).

The management of acute behavioural disturbance in schizophrenia and related disorders

The management of the acutely disturbed psychotic person requires calm strategies that protect the safety and dignity of all concerned. The first step should be to try to engage the person and understand what is driving their agitation. Sometimes simple measures such as orienting and explaining what is happening can be enough to defuse the situation. The opportunity should be taken to perform a cognitive screen to exclude delirium/intoxication and also, where possible, physical examination, blood tests, urinary drug screen and an electrocardiogram (ECG).

Attention should be paid to the physical environment, such that stimulation is reduced and safety ensured. Objects that might be thrown or used as weapons should be removed, where possible. An escape route should be made available by ensuring that the exit doorway is not blocked. Back-up should be available and staff should know where duress alarms are situated.

If several staff are involved, ensure one person takes control of the situation and orchestrates matters, with clear communication as to each individual's role. One person should communicate with the agitated individual in a clear even voice. The individual should be offered reassurance that they are safe and that the intent is to ensure the safety of all concerned. Interventions need to be carefully explained and a rationale provided.

Always try to defuse the situation by careful negotiation. The following techniques can be useful:

- Ventilation: allowing the opportunity to express fears, frustration, anger
- Redirection: exploring solutions to allow the person to gain control
- Time out: offering the person a low stimulus environment, for example, their bedroom or a similar quiet environment to assist them to gain control.

If physical restraint is required, ensure sufficient trained staff are available. If medication is used, the person needs to be informed about what the medicine is and the rationale for its use. Seclusion is rarely required but, if employed, should be used for as short a time as possible and local procedures need to be followed. At a reasonable time interval after restraint or seclusion, the person should be offered the opportunity to debrief about the incident. Service protocols should be reviewed regularly in the light of both recent research and local experience.

If non-pharmacological approaches have been unsuccessful, pharmacological management may be needed (see Figure 2).
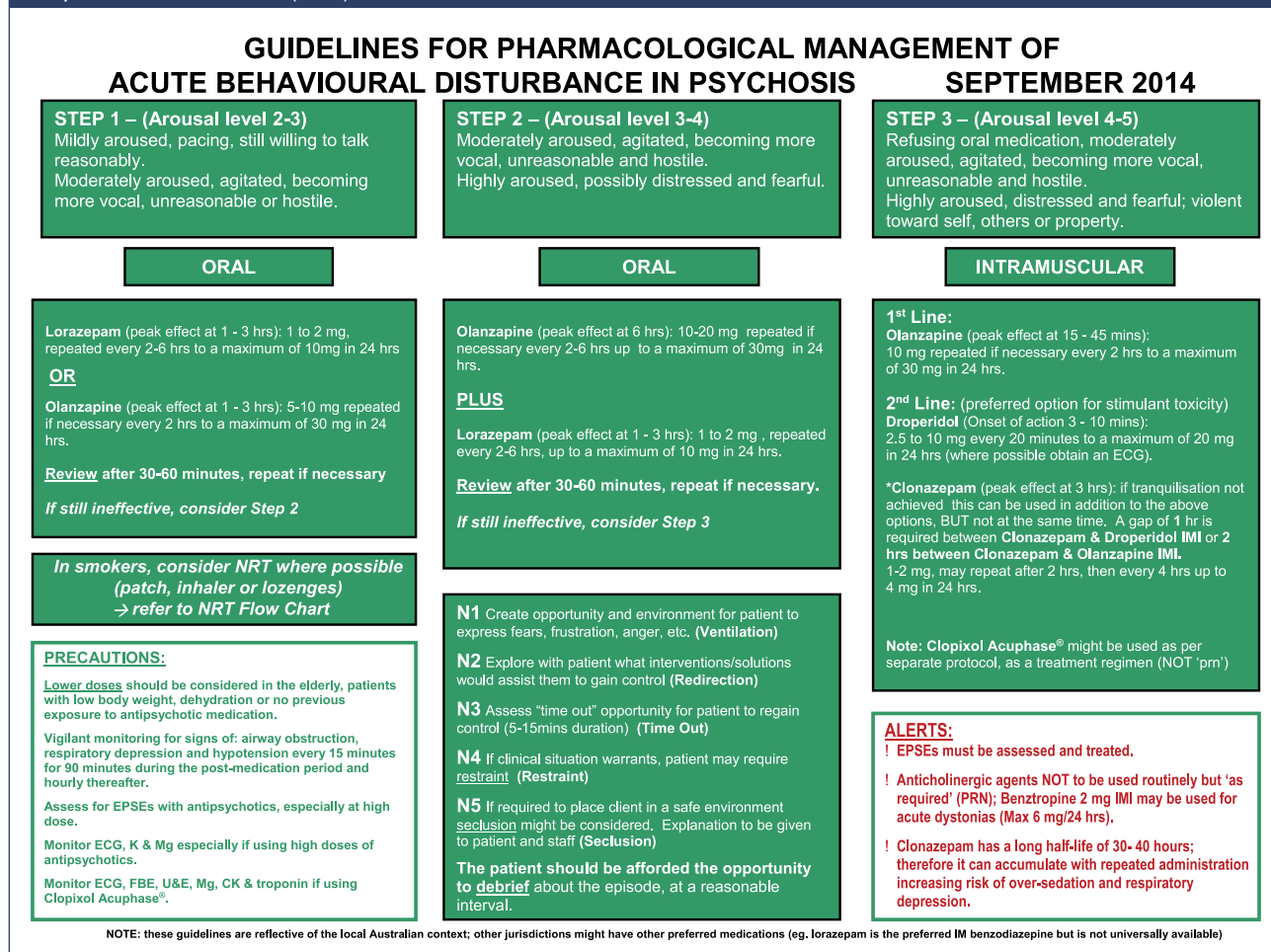
A number of antipsychotic drugs, including olanzapine (10–20 mg), risperidone (2–6 mg), quetiapine (300–800 mg) and aripiprazole (5–30 mg), have been shown to be effective for acute agitation (Kinon et al., 2008; Zeller and Rhoades, 2010). Often, a benzodiazepine, such as lorazepam, is also given. Particular care should be taken with midazolam because of the risk of respiratory depression. Oral administration of medication is preferable, but if this is not possible, intramuscular preparations may be used. Intramuscular olanzapine and benzodiazepines should not

Recommendations on medication for acute behavioural disturbance	Type	Level of evidence
Manage acute behavioural disturbance using the least restrictive measures necessary for the safety of the patient and other people.	CBR	N/A
Oral agents (including wafers) are preferable to medications given by injection.	CBR	N/A
If parenteral antipsychotic agents are required, second-generation antipsychotic agents are preferred.	EBR	II
If 'as required' (PRN) antipsychotic medication is used for acute psychosis, monitor closely to avoid overdosing, and consider the adverse effects of polypharmacy.	EBR	III-1
Lower psychotropic doses should be considered in the elderly, people of Asian ethnicity and people with low body weight, dehydration or no previous exposure to antipsychotic medication.	EBR	II
Extrapyramidal side effects must be closely monitored and treated appropriately. Anticholinergic agents should not be used routinely but PRN.	EBR	III-2

CBR: consensus-based recommendation; EBR: evidence-based recommendation.
N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

Figure 2. Flowchart for the pharmacological management of acute behavioural disturbance in psychosis. Barnes et al., (2002). Adapted from Castle et al., (2012).

GUIDELINES FOR PHARMACOLOGICAL MANAGEMENT OF ACUTE BEHAVIOURAL DISTURBANCE IN PSYCHOSIS   SEPTEMBER 2014

STEP 1 – (Arousal level 2-3)
Mildly aroused, pacing, still willing to talk reasonably.
Moderately aroused, agitated, becoming more vocal, unreasonable or hostile.

STEP 2 – (Arousal level 3-4)
Moderately aroused, agitated, becoming more vocal, unreasonable and hostile.
Highly aroused, possibly distressed and fearful.

STEP 3 – (Arousal level 4-5)
Refusing oral medication, moderately aroused, agitated, becoming more vocal, unreasonable and hostile.
Highly aroused, distressed and fearful; violent toward self, others or property.

ORAL

ORAL

INTRAMUSCULAR

Lorazepam (peak effect at 1 - 3 hrs): 1 to 2 mg, repeated every 2-6 hrs to a maximum of 10mg in 24 hrs

OR

Olanzapine (peak effect at 1 - 3 hrs): 5-10 mg repeated if necessary every 2 hrs to a maximum of 30 mg in 24 hrs.

Review after 30-60 minutes, repeat if necessary

If still ineffective, consider Step 2

In smokers, consider NRT where possible (patch, inhaler or lozenges) → refer to NRT Flow Chart

PRECAUTIONS:
Lower doses should be considered in the elderly, patients with low body weight, dehydration or no previous exposure to antipsychotic medication.

Vigilant monitoring for signs of: airway obstruction, respiratory depression and hypotension every 15 minutes for 90 minutes during the post-medication period and hourly thereafter.

Assess for EPSEs with antipsychotics, especially at high dose.

Monitor ECG, K & Mg especially if using high doses of antipsychotics.

Monitor ECG, FBE, U&E, Mg, CK & troponin if using Clopixol Acuphase®.

Olanzapine (peak effect at 6 hrs): 10-20 mg repeated if necessary every 2-6 hrs up to a maximum of 30mg in 24 hrs.

PLUS

Lorazepam (peak effect at 1 - 3 hrs): 1 to 2 mg , repeated every 2-6 hrs, up to a maximum of 10 mg in 24 hrs.

Review after 30-60 minutes, repeat if necessary.

If still ineffective, consider Step 3

N1 Create opportunity and environment for patient to express fears, frustration, anger, etc. **(Ventilation)**

N2 Explore with patient what interventions/solutions would assist them to gain control **(Redirection)**

N3 Assess "time out" opportunity for patient to regain control (5-15mins duration) **(Time Out)**

N4 If clinical situation warrants, patient may require restraint **(Restraint)**

N5 If required to place client in a safe environment seclusion might be considered. Explanation to be given to patient and staff **(Seclusion)**

The patient should be afforded the opportunity to debrief about the episode, at a reasonable interval.

1st Line:
Olanzapine (peak effect at 15 - 45 mins):
10 mg repeated if necessary every 2 hrs to a maximum of 30 mg in 24 hrs.

2nd Line: (preferred option for stimulant toxicity)
Droperidol (Onset of action 3 - 10 mins):
2.5 to 10 mg every 20 minutes to a maximum of 20 mg in 24 hrs (where possible obtain an ECG).

***Clonazepam** (peak effect at 3 hrs): if tranquilisation not achieved this can be used in addition to the above options, BUT not at the same time. A gap of **1** hr is required between **Clonazepam & Droperidol IMI** or 2 hrs between **Clonazepam & Olanzapine IMI.**
1-2 mg, may repeat after 2 hrs, then every 4 hrs up to 4 mg in 24 hrs.

Note: Clopixol Acuphase® might be used as per separate protocol, as a treatment regimen (NOT 'prn')

ALERTS:
! **EPSEs must be assessed and treated.**

! Anticholinergic agents NOT to be used routinely but 'as required' (PRN); Benztropine 2 mg IMI may be used for acute dystonias (Max 6 mg/24 hrs).

! Clonazepam has a long half-life of 30- 40 hours; therefore it can accumulate with repeated administration increasing risk of over-sedation and respiratory depression.

NOTE: these guidelines are reflective of the local Australian context; other jurisdictions might have other preferred medications (eg. lorazepam is the preferred IM benzodiazepine but is not universally available)

be given together because there is a risk of respiratory depression with this combination. In selecting the type and dose of medications, individual factors such as the person's ethnicity, whether they are drug naive and current medications and substance use must be taken into account.

Nicotine transdermal patches may be helpful in reducing agitation and aggression in smokers with schizophrenia if they are prevented from smoking in hospital (Allen et al., 2011). This finding reinforces the importance of establishing whether people are smokers and considering whether some agitation might be due to nicotine withdrawal.

Catatonia is a rare condition that can occur in both schizophrenia and mood disorders (Grover et al., 2015). While retarded catatonia is more common, excited catatonia may occasionally present as an acute behavioural disturbance. Catatonia should be treated with IV lorazepam or emergency ECT (Sienaert et al., 2014).

Neurostimulation therapies

Electroconvulsive therapy (ECT). A Cochrane review (Tharyan and Adams, 2005) concluded that ECT, either alone or added to antipsychotic medication, resulted in increased rates of global improvement and faster rates of symptomatic improvement than sham ECT or placebo in people with schizophrenia. ECT may have a particular role in the management of treatment-resistant schizophrenia, although there are few studies. A small randomised sham-controlled trial of ECT in treatment-resistant schizophrenia (Goswami et al., 2003) found no clear advantage for active ECT, but open studies suggest that adding ECT to antipsychotic agents is a safe and potentially useful strategy for people with treatment-resistant schizophrenia (Braga and Petrides, 2005; Chanpattana and Sackeim, 2010). The combination of ECT with clozapine may be of particular benefit for people who have an inadequate response to clozapine alone (Havaki-Kontaxaki et al., 2006; Petrides et al., 2015).

Any advantage of adding ECT to antipsychotic medication, compared with antipsychotic medication alone, is no longer evident within 6–8 weeks of ceasing ECT, despite ongoing antipsychotic treatment (Tharyan and Adams, 2005). In the only RCT of continuation ECT in people with treatment-resistant schizophrenia who had responded to the combination of ECT and antipsychotic medication, rates of relapse were much

guide.medlive.cn

lower with the combination of ECT and antipsychotics, compared with either treatment alone (Chanpattana et al., 1999).

In a limited analysis of data from studies comparing bitemporal and unilateral ECT, Tharyan and Adams (2005) found no clear advantage for either electrode placement. Recent data suggest that bifrontal ECT may be more effective than bitemporal ECT in people with schizophrenia and schizoaffective disorder, with the added benefit of causing less cognitive impairment (Phutane et al., 2013). This finding is yet to be replicated. One randomised study observed a more rapid response in people treated with bitemporal ECT at doses two and four times seizure threshold, compared with treatment at the seizure threshold, but there was no difference in outcome at the end of the course (Chanpattana et al., 2000). Ultra-brief ECT is likely to have significant advantages in reducing cognitive side effects, although its efficacy in schizophrenia is unproven. There has been one case report of the successful use of right unilateral ultra-brief ECT in the treatment of catatonic schizophrenia (Cupina et al., 2013).

There has been a traditional view that prolonged courses of ECT (up to 20 index treatments) are required for people with schizophrenia. However, in RCTs where ECT has been demonstrated to be of benefit in combination with medication, 8–12 index treatments were efficacious (Abraham and Kulhara, 1987; Brandon et al., 1985; Taylor and Fleminger, 1980). Given the relationship between bitemporal ECT and

---

Key consideration

ECT may be of value when used in combination with antipsychotic medications, both in the treatment of acute schizophrenia and in treatment-resistant schizophrenia.

ECT: electroconvulsive therapy.

Recommendations on electroconvulsive therapy	Type	Level of evidence
The prescription of an index course of ECT for the treatment of schizophrenia may be considered in combination with antipsychotic medication when a rapid clinical response is an urgent priority.	EBR	II
The addition of ECT may be considered in people with treatment-resistant schizophrenia who have an inadequate response to clozapine.	EBR	II
Prolonged courses of ECT without measured improvement are not recommended for people with schizophrenia because most research suggests that response occurs within 12 treatments. For a minority of individuals, longer courses may be required if progressive improvement occurs with each treatment.	EBR	III
Right unilateral, bifrontal and bitemporal electrode placements may all be considered in the treatment of schizophrenia.	EBR	II
In general, unilateral ECT should be prescribed at 3–6 times seizure threshold. Bitemporal and bifrontal ECT should generally be prescribed at 1.5 times seizure threshold.	CBR	N/A
If index ECT is effective for an individual, consider prescribing a course of continuation ECT for at least 6 months, in combination with antipsychotic medication. ECT should be given weekly for 1 month, then every 2 weeks, with flexibility according to response and side effects.	CBR	N/A
An objective rating scale should be used to assess baseline symptom severity, response during the ECT course and outcome at completion of a course of ECT.	CBR	N/A

EBR: evidence-based recommendation; CBR: consensus-based recommendation.
N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

---

increased cognitive adverse effects in the treatment of depression, careful consideration of the benefits and risks is warranted before prescribing prolonged index courses of bitemporal ECT (Dunne and McLoughlin, 2012; Phutane et al., 2013; Sackeim et al., 2006). The adverse cognitive effects of ECT in people with schizophrenia appear to be consistent with those observed in the treatment of depression. However, detailed studies in people with schizophrenia are lacking. Available evidence suggests that positive rather than negative symptoms predominantly respond to ECT (Chanpattana and Sackeim, 2010). The use of an objective rating scale to assess symptom severity and quantify response is strongly recommended.

Repetitive transcranial magnetic stimulation. There is some evidence for the efficacy of active low frequency (≤1 Hz) repetitive transcranial magnetic stimulation (rTMS) applied to the temporo-parietal cortex in treating auditory hallucinations (Zhang et al., 2013b). There is also limited evidence for the efficacy of rTMS applied to the left dorsolateral prefrontal cortex to treat negative symptoms of schizophrenia (Freitas et al., 2009; Prikryl et al., 2007). Given that rTMS

guide.medlive.cn

is generally well tolerated, a trial of rTMS is a low risk strategy with some possibility of benefit.

Transcranial direct current stimulation. The use of transcranial direct current stimulation (tDCS) to treat schizophrenia is still in the research phase. There is preliminary evidence that tDCS may have benefits in treating auditory verbal hallucinations, and positive and negative symptoms of schizophrenia generally (Brunelin et al., 2012), although these results need further replication. Research is underway to evaluate the potential role of tDCS in cognitive remediation in schizophrenia, when given concurrently with cognitive training exercises (Tarur Padinjareveettil et al., 2014).

Psychological and psychosocial therapies

Overview. There is a growing evidence base to support the use of psychotherapy and psychosocial strategies for psychosis. These should be provided along with optimal antipsychotic medication. There is clear evidence for CBT for psychosis and cognitive remediation, with an emerging evidence base for other therapies (Lyman et al., 2014; Wykes et al., 2008, 2011). This trend is likely to continue, given clinicians' appreciation of the limits of pharmacotherapy in addressing all the domains of schizophrenia and the current focus on person-centred, individualised care.

The therapeutic relationship is the cornerstone of effective treatment. All clinicians working with people with schizophrenia need psychological skills. Services should ensure that clinicians can spend time delivering psychological therapies. People living with psychosis may have experienced many losses, traumas and hardships, and rejection by others and by society. Clinicians must acknowledge these painful aspects of the person's life and respond empathically. A promising new possibility is to draw on techniques from positive psychology to enhance positive mental health and wellbeing. Much of the work of the growing non-government sector has begun to focus on this aspect but more research, skill development and training is required. It is important for clinicians to expand their mindset and role to accommodate these new developments.

Potential barriers to offering psychological and psychosocial therapies include the limited tenure of admission to a specialist mental health service, the frequent rotation and turnover of clinicians, the possible limitations on time spent with individuals and families, the fragmentation of the clinical and non-government services, and the lack of training in psychological therapies.

Cognitive function. Cognitive deficits need to be taken into account in planning psychosocial treatments for the individual. Eight cognitive domains are commonly (but not uniformly) impaired in people living with schizophrenia:

- Speed of processing
- Attention/vigilance
- Working memory (non-verbal)
- Working memory (verbal)
- Verbal learning
- Visual learning
- Reasoning and problem solving
- Social cognition, defined as the combination of facial affect recognition, social perception and processing, theory of mind and social attributions (Nuechterlein et al., 2008a).

Impairment in these domains influences functional capacity and limits functional outcomes, either directly or by moderating other variables. For example, working memory and attention have direct effects on work, executive skills and interpersonal behaviour. A distinction can be made between functional capacity and performance, with some cognitive domains necessary to improve skills (verbal memory and executive functions), while other functions relate to competence (e.g. processing speed and attention/working memory associated with social competence) (Bowie et al., 2008). Processing speed underpins performance in other domains and appears to be the core impairment in skill acquisition and everyday functional performance.

Several tools for cognitive screening, which were developed for research purposes, have been considered for routine clinical use to enable clinicians to assess the cognitive dimension of the illness and to interpret and apply this knowledge to treatment plans (Velligan et al., 2004). The Brief Cognitive Assessment (BCA) (Velligan et al., 2004) and the Brief Cognitive Assessment Tool for Schizophrenia (B-CATS) (Hurford et al., 2011) have sound psychometric properties and good correlations with functional measures and can be completed in 15 minutes. The Brief Assessment of Cognition in Schizophrenia (BACS) battery has good psychometric properties, has alternate forms to minimise practice effects and the composite score relates strongly to functional measures (Keefe et al., 2006a). In the future, cognitive screens suitable for clinical use may be available via smart technology. Cognitive assessment should take place as part of the initial assessment (once the acute symptoms have settled) and before and after specific interventions.

Ideally, mental health services for people with schizophrenia would have access to a neuropsychologist experienced in psychosis who could provide comprehensive neurocognitive testing and sophisticated interpretation of results. However, this is uncommon in clinical practice. More routinely, multidisciplinary teams have access to occupational therapists skilled in administration and interpretation of the Allen's Cognitive Level Scale, which correlates well with neuropsychological tests and can be used to guide care plans (Su et al., 2011).

Clinically, the focus should be on improving cognitive functioning in the service of improving functional competency in the 'real world'. A number of interview-based cognitive measures have been developed with arguably more face validity with regard to cognitive function. The Schizophrenia

guide.medlive.cn

Cognition Rating Scale (SCoRS) (Keefe et al., 2006b) and the Cognitive Assessment Interview (CAI) (Ventura et al., 2010) have been found to relate well to performance-based measures of cognition. These measures have also been found to explain variance in real-world functioning not explained by standard cognitive batteries.

Psychoeducation. Psychoeducation programmes for people with schizophrenia improve adherence to treatment and lead to better outcomes, better management of subsequent relapse, lower readmission rates and a greater sense of wellbeing (Xia et al., 2011). In the early phases, psychoeducation tends to focus on support and educating the person with schizophrenia and their family about the illness, using a biopsychosocial perspective. As the individual recovers, the subject matter may evolve to more general topics, such as life skills (Medalia and Revheim, 2002). Provided consent is given, information should also be given to others who are in contact with the person with schizophrenia. These may include staff of community agencies, NGOs and supported accommodation residences.

Illness self-management training. Illness self-management training is concordant with the recovery model in providing access to knowledge to allow informed decision-making as well as teaching strategies to assist in medication adherence and relapse prevention. Core components of training include psychoeducation, behavioural interventions to facilitate adherence, coping strategies for residual symptoms and a relapse prevention plan (Mueser et al., 2013).

There are many different evidence-based peer-delivered programmes. Wellness recovery action planning (WRAP) (Cook et al., 2012) and the Illness Management and Recovery (IMR) programme (Mueser and Gingerich, 2011) have the most evidence for effectiveness.

Family support and psychoeducation. Families of people with schizophrenia experience tremendous distress, grief and chronic day-to-day stress, which can be extreme and result in significant risks to their health and wellbeing. These issues have generally been neglected by services and by many health professionals – yet effective support for families is crucial, since for many people with schizophrenia,

Recommendations on illness self-management, family support and psychoeducation	Type	Level of evidence
Wellness recovery action planning, the Illness Management and Recovery programme or a similar peer education programme should be made available.	EBR	I
An educational programme that promotes the person actively managing their own recovery should be a core component of service delivery.	EBR	I
Psychoeducation for people with schizophrenia reduces relapse (probably through improved adherence), increases satisfaction with treatment and improves knowledge. Psychoeducation should be offered as a core intervention.	EBR	II
Family psychoeducation is effective and should be offered routinely in the comprehensive care of schizophrenia.	EBR	I

EBR: evidence-based recommendation.

survival and recovery depend on their family relationships. Families deserve involvement and support from professionals wherever possible.

The link between family burden and distress and outcomes for the person with schizophrenia has led to the recognition that optimal care should include significant others in the individual's recovery environment, particularly their family. Multiple programmes and modalities (individual versus group) have been empirically validated (McFarlane, 2002; Pilling et al., 2002). Common elements include education about the illness and coping strategies (Sin and Norman, 2013).

Peer workers. Many services now employ peer workers as part of the clinical team, or engage them as clinical consultants (Nestor and Galletly, 2008). Peer workers can assist with motivation, building confidence and improving social interaction (Henderson and Kemp, 2013). There is a rise in peer-delivered therapies such as voice hearer groups and strengths-based interventions (Romme and Escher, 2012).

Peers are also delivering lifestyle interventions, such as quit-smoking groups (Ashton et al., 2013). A recent Cochrane review concluded that involving peer workers (also called consumer-providers) in mental health teams results in psychosocial, mental health symptom and service use outcomes for clients that were no better or worse than those achieved by professionals employed in similar roles, particularly for case management services (Pitt et al., 2013). There is low-quality evidence that involving consumer-providers in mental health teams results in a small reduction in clients' use of crisis or emergency services. These workers generally receive training through educational courses, often run by NGOs. Their lived experience can be very valuable, especially for young people with FEP.

CBT for psychosis. CBT for people with psychosis (CBTp) has emerged as an evidenced-based treatment usually used as an adjunct to pharmacotherapy to reduce the distress and disability associated with residual or persistent psychotic

guide.medlive.cn

symptoms. CBTp is more effective than other talking therapies such as supportive counselling for hallucinations, and there may be long-term advantages for CBTp in dealing with emotional distress and depression, but advantages over other therapies for overall mental state and delusions are not established (Jauhar et al., 2014; Jones et al., 2012; Van der Gaag et al., 2014). The low risks and broad potential symptom targets of CBTp have resulted in its use in both FEP and persistent illness. A multicentre RCT of CBTp in people at risk of psychosis reported lowered symptom severity but no impact on rates of transition to psychosis (Morrison et al., 2004).

Although positive symptoms were the initial targets of CBTp, research has also been conducted using CBTp for negative symptoms and for comorbid depression, anxiety and substance use (Wykes et al., 2008).

Cognitive remediation therapy and compensation. Cognitive remediation aims to improve cognitive processes (attention, memory, executive function, social cognition or meta-cognition). There is emerging evidence of associated improved real-world function (Wykes et al., 2011), but the outstanding issues for further research include the mechanisms of change and ensuring real-world transfer. A number of cognitive remediation programmes are available online, although not all of these programmes have been evaluated. The evidence to date relies on programmes facilitated by clinicians trained in cognitive remediation therapy (CRT).

CRT has been used at all stages of illness including at-risk states, early psychosis and in people with established illness. When combined with vocational rehabilitation, CRT is associated with an increase in hours worked and job retention (McGurk and Wykes, 2008).

Compensatory strategies, as distinct from remediation, can also be useful (e.g. diaries, calendar, mobile phone reminders and environmental modifications). A manualised form of compensatory strategies, '*cognitive adaptation therapy*', should be considered, particularly if there is no access to CRT or the individual prefers to utilise cognitive adaptation therapy (Velligan et al., 2008).

Emerging psychological and psychosocial therapies

Social cognition therapy. Social cognition is defined as '*the ability to construct representations of the relations between oneself and others, and to use those representations flexibly to guide social behaviours*' (Adolphs, 2001). Components of social cognition include theory of mind (the ability to infer other's mental states), emotional and social perception and social attribution biases. Impairment in social cognition is a separate domain of pathology, independent of positive symptoms and only partially accounted for by negative symptoms and impairment in neurocognition.

People with schizophrenia generally have impairments in social cognition. A number of social cognition remediation programmes have been developed, including the SoCog programme (Marsh et al., 2013) and Social Cognition and Interaction Training (Combs et al., 2007; Roberts et al., 2014). Evaluations of these programmes have been encouraging, especially in regards to improving emotional perception (Kurtz et al., 2012; Kurtz and Richardson, 2011). The association of both neurocognition and social cognition with community function has resulted in programmes integrating the two therapies, for example, cognitive enhancement therapy (Eack et al., 2013; Hogarty et al., 1997).

Acceptance and commitment therapy and mindfulness-based therapies for psychosis. Third-wave CBTs, including ACT and mindfulness groups, aim to modify the person's relationship with their psychotic experiences (Khoury et al., 2013). A key premise is that attempting to suppress mental events can paradoxically bring these experiences into the foreground. These therapies promote an alternate stance of noticing the experiences, non-judgementally and without struggle, to reduce the extent to which they dominate the person's experience and behaviour. Both involve teaching meta-cognitive awareness, meditation and mindfulness skills. ACT also focusses on the person's goals and values. ACT is supported by some RCT evidence (Gaudiano and Herbert, 2006; Shawyer et al., 2012), but it remains unclear when or for whom these approaches might be particularly indicated. An Australian trial of ACT in psychosis is currently underway (Thomas et al., 2014).

Meta-cognitive training. Meta-cognitive training (MCT) is a therapy influenced by CBT and CRT approaches to psychosis (Moritz et al., 2010). MCT focusses more on the process of thinking, especially cognitive biases, rather than the content. Therapy is usually in a small group psychoeducation based format with additional individual sessions. Early studies have found improvement in positive symptoms and self-efficacy (Balzan et al., 2014; Moritz et al., 2014).

Other therapies. Other therapies requiring more research and evaluation include the following:

- Art therapy is included in the UK NICE clinical guideline on the treatment and management of psychosis and schizophrenia in adults (NICE, 2014), but RCT evidence is inconclusive (Crawford, 2012).
- Music therapy has a long history in schizophrenia and recent trials support its efficacy in social domains and quality of life (Grocke et al., 2009, 2014; Mössler et al., 2011).
- Narrative therapy aims to promote the development of positive personal narratives along with competence and a sense of control over one's life (Dickerson and Lehman, 2011). There are several forms of narrative therapy including some that integrate CBT techniques.

guide.medlive.cn

This approach is congruent with the emphasis on the person and their subjective experience (Strauss, 2013).

- Solution-focussed therapy is an approach that is not specific for any particular condition but has been used in a range of mental health conditions. The approach is concordant with a recovery approach, reducing the emphasis on problems and focussing on future opportunities.

Key consideration
Comprehensive care of people living with schizophrenia requires an integration of biological and psychosocial interventions. Psychopharmacology with standard case management does not address all the domains of the illness, especially cognitive deficits, social complications and functional impairment.

Recommendations on the use of cognitive therapies	Type	Level of evidence
People with schizophrenia and their carers should receive psychoeducation about the impact of the illness on cognition and function.	EBR	I
Services for people with schizophrenia should implement routine use of cognitive screening tools that are sensitive to the cognitive profile in schizophrenia.	CBR	N/A
Cognitive remediation therapy (CRT) and cognitive compensatory techniques should be available to anyone with schizophrenia who has cognitive impairment.	EBR	I
Consider providing integrated social cognitive therapies and cognitive remediation to optimise functional outcomes.	EBR	II
Cognitive behaviour therapy (CBT) should be routinely available, especially when an individual's positive symptoms are slow to respond or refractory to drug treatment.	EBR	I
Acceptance and commitment therapy (ACT) should be considered for people who have already received CBTp and continue to be distressed or disabled by symptoms.	CBR	N/A
Intervention programmes addressing social cognition (e.g. meta-cognitive training, social skills training and/or SoCog) should be available to improve social function.	EBR	II
If therapies without a strong evidence base are used in clinical practice, they should be formally evaluated to assess benefit and monitor any adverse outcomes.	CBR	N/A

CBR: consensus-based recommendation; EBR: evidence-based recommendation; CBTp: CBT for people with psychosis.
N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

- Sensory modulation/integration therapy has been used in occupational therapy since the 1970s. More recent modifications have led to a renewed interest in its application to schizophrenia, especially to reduce seclusion and restraint (Chalmers et al., 2012).
- Open Dialogue, developed in Finland by Seikkula (2002), focusses on the social network and on establishing a therapeutic dialogue. Further research would be needed to provide evidence to support this approach.

Vocational rehabilitation

The desire to work in the open labour market is often a priority for people with psychotic illness (Morgan et al., 2011; Waghorn et al., 2012). Vocational rehabilitation aims to improve economic and social participation. There are two main models (Drake et al., 1999, 2003, 2012):

- Prevocational training – training is provided during a period of preparation before the person seeks competitive employment
- Supported employment – people are placed in competitive employment with on-the-job support.

A Cochrane review (Kinoshita et al., 2013) found that supported employment was more effective than other strategies (including prevocational training) in improving vocational outcomes relevant to people with severe mental illness. The most effective form of supported employment was individual placement and support. On average, 60% of people given individual placement and support returned to employment, compared with 25% in the various control groups (Bond et al., 2012).

Trials of individual placement and support in FEP have extended vocational outcomes to include education, which has boosted vocational outcomes, with approximately 85% returning to school or work (Killackey et al., 2008). The addition of targeted CRT can further enhance rates of attaining and retaining work among people with schizophrenia (McGurk and Wykes, 2008).

The lack of effective vocational rehabilitation services is a major deficit in many mental health services. Lack of employment has serious consequences in terms of self-esteem, income, personal growth and social inclusion. In general, job agencies, even those with an interest in rehabilitation of people with disabilities, are not effective in getting people with

Key consideration
Individual placement and support is the most successful form of vocational rehabilitation for people with psychotic disorders.

Recommendations regarding vocational rehabilitation	Type	Level of evidence
People with schizophrenia should be encouraged to find a meaningful occupation, either paid or voluntary. This should be actively facilitated by the clinician and specific programmes to deliver this intervention need to be widely established.	EBR	I
People should be linked into agencies which provide vocational rehabilitation services early in the illness.	CBR	N/A
In planning new services, or developing existing services, vocational recovery specialists should be included in the treating team.	CBR	N/A

EBR: evidence-based recommendation; CBR: consensus-based recommendation.
N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

schizophrenia into the workforce. As with so many other aspects of care, specialised services for people with schizophrenia, integrated into the mental health services, are needed.

For a discussion of the right to work for people with psychosis, refer to '*Meaningful lives. Supporting young people with psychosis in education, training and employment*' (International First Episode Vocational Recovery Group, 2008).

Involuntary treatment

Schizophrenia is often associated with poor recognition of the origin of symptoms and the need for treatment. The main purpose of mental health laws is to allow for the involuntary treatment of people who do not recognise the need for that treatment, while safeguarding the rights of the mentally ill. Improving the person's capacity to make sound treatment decisions is an objective of the recovery model of care, and an important function of mental health laws is to allow treatment in order to restore the capacity to make rational decisions in people who have temporarily lost that capacity.

The mental health laws of the states and territories of Australia and in New Zealand are mainly concerned with protecting individuals from harming themselves and others. A further consideration in some laws is to allow treatment of people who have serious impairment in their capacity for self-care. Never-treated psychosis is associated with a

greatly increased rate of self-harm and violence (Nielssen and Large, 2010), and a long duration of untreated psychosis is associated with less complete recovery. Hence, involuntary treatment may be indicated for people in the first episode of psychosis who cannot be persuaded to have a trial of treatment with antipsychotic medication. Involuntary treatment may also be warranted for people who have previously responded to treatment but have experienced a relapse of illness and no longer recognise the need for treatment.

One of the challenges in clinical practice is the consideration of when or whether involuntary treatment, either in hospital or in a community setting, is helpful for a person's recovery. Forming a therapeutic alliance can be difficult when working with people who have had adverse experiences of involuntary treatment and treatment with antipsychotic medication. Decisions to invoke involuntary treatment should consider the person's best interests and their perception of the value of treatment when they are well, if possible, in the form of an advance directive to their carers.

Although community treatment orders (CTOs) have been associated with controversy regarding both ethics and efficacy, Australia has one of the highest rates of CTOs in the world, with as many as 10% of people with schizophrenia on a CTO (Light et al., 2012). On balance, there is some evidence to suggest that involuntary community treatment may be helpful for people with schizophrenia when there have been difficulties with voluntary engagement with

Key consideration
Involuntary treatment of people with first-episode psychosis who persistently refuse treatment, and people who have had a previous psychotic episode and experienced a relapse that is likely to respond to treatment, may reduce the likelihood of serious harm and improve outcome.

Recommendations on involuntary treatment	Type	Level of evidence
The aim of involuntary treatment should be to restore the person's capacity to make rational treatment decisions.	CBR	N/A
The person's best interests, as well as their wishes and the content of advanced directives, should be considered in any decisions to invoke mental health laws.	CBR	N/A
The use of involuntary treatment for people with schizophrenia must adhere to local legislation.	CBR	N/A

CBR: consensus-based recommendation.
N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

guide.medlive.cn

services and there has been a pattern of harmful behaviour or serious functional impairment associated with exacerbations of illness after refusing treatment. Involuntary community treatment is not a substitute for effective person-centred care but is a way to facilitate engagement in treatment to prevent worse outcomes. Treatment plans that form the justification for any CTO should include information regarding the individual's wishes in the form of previous advance directives and collaborative recovery plans.

Section 4. Physical health

Metabolic syndrome and obesity

People with schizophrenia have significantly higher than expected rates of ischaemic heart disease, cerebrovascular disease and diabetes. In the second Australian National Survey of Psychosis (Morgan et al., 2011), 53% of participants aged 18–64 years met criteria for metabolic syndrome, including at-risk levels of abdominal obesity (82%), high-density lipoproteins (50%), triglycerides (48%) and hypertension (49%). About one-quarter were at high risk of a cardiovascular event in the next 5 years. Less than half of those with known hypertension, hyperglycaemia or elevated cholesterol were receiving medication for these conditions (Galletly et al., 2012).

Metformin may reduce the risk of obesity and diabetes (Correll et al., 2013), but can be associated with Vitamin B12 deficiency. Statins, antihypertensive medicines and other evidence-based treatments for metabolic conditions should be prescribed as indicated. Many mental health services now undertake cardiometabolic monitoring (Stanley and Laugharne, 2014). It is essential that this is linked to effective treatment, generally involving close liaison with primary care (which may be co-located with the community mental health service). Another option is for psychiatrists to take responsibility for at least some of the necessary investigations and prescribing of medications for physical conditions, with referral to specialised medical services as needed. This may require some up-skilling but is no more complicated than managing lithium or clozapine.

Lifestyle interventions must take into account the cognitive dysfunction, impaired motivation and energy, and low income of most people with schizophrenia. The second Australian National Survey of Psychosis (Morgan et al., 2012) found that the majority of participants reported very low levels of physical activity, so exercise needs to start at an appropriate level. There is evidence that an 18-month behavioural weight loss programme can assist people with schizophrenia to lose weight (Daumit et al., 2013). Baker et al. (2015) reported some improvements with an intervention targeting both smoking and cardiovascular risk factors in people with psychotic disorders, but much more research and evaluation is urgently needed to find effective interventions that can be widely adopted across mental health services (Gates et al., 2015).

The importance of holistic preventive health care in people with FEP is described in the HeAL consensus statement 2013 (available at: http://www.iphys.org.au). Information about managing cardiometabolic effects of antipsychotic medication in people with FEP is found in Positive Cardiometabolic Health: an early intervention framework for patients on psychotropic medication, NSW Government Health Education Training Institute (2011) (available at www.heti.nsw.gov.au/cmalgorithm).

Smoking

The second Australian National Survey of Psychosis found that two-thirds of participants were current smokers and 81% had a lifetime history of smoking (Cooper et al., 2012). There has been no change in the prevalence of smoking among people with schizophrenia between 1999 and 2010 (Morgan et al., 2012), indicating that general population measures such as media advertisements and telephone support lines are ineffective for this group of people.

However, both individual and group smoking cessation programmes that are specifically tailored to the needs of people with schizophrenia can be helpful (Bennett et al., 2013). Group treatment programmes involving peer workers have been shown to be effective in Australian mental health services (Ashton et al., 2015). Nicotine replacement therapy is often useful. Simple guidelines are available for the management of smoking in people with schizophrenia (Mendelson et al., 2015). Smoking increases the metabolism of some antipsychotic agents, and doses may need to be reduced when people quit smoking (see '*Smoking and antipsychotic medication*' in '*Section 3. Treatment: context, structure and content of interventions*').

Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is a breathing disorder characterised by repeated collapse and obstruction of the upper airway, causing nocturnal hypoxia and sleep arousals (Patil et al., 2007a). Symptoms include non-rejuvenating sleep, daytime hyper-somnolence, cognitive impairment, morning headaches, dry mouth, nocturia, snoring and breathing pauses during sleep (Lal et al., 2012; Patil et al., 2007a). People with schizophrenia have a high prevalence of OSA risk factors including obesity, smoking, alcohol consumption and hypnotic medication use (Al Lawati et al., 2009; Galletly et al., 2012). OSA is associated with an increased risk of stroke, cardiac arrhythmias, heart failure, diabetes, hypertension, cardiovascular disease and motor vehicle accidents (Al Lawati et al., 2009; Drager et al., 2013; Gami et al., 2013; Kendzerska et al., 2014).

OSA may be more likely, and less detectable, among people with schizophrenia in whom sleep disturbance, hyper-somnolence and cognitive impairment may be mistaken for negative symptoms of schizophrenia or medication side effects. A systematic review found that the prevalence of OSA varied from 1.6% to 52%; OSA was associated with male gender, age > 50 years and obesity

(Myles et al., 2016). It is imperative to assess for OSA by questioning about daytime somnolence, snoring and breathing pauses. If OSA is suspected, the person should be referred to a respiratory physician or sleep physician.

The treatment of OSA is non-invasive nocturnal ventilation, usually via continuous positive airway pressure (CPAP). CPAP has been demonstrated in controlled trials to improve sleep symptoms and improve blood pressure and

heart failure in people with sleep apnoea (Gami et al., 2013; Kendzerska et al., 2014), but as yet there are no published trials of CPAP in people with schizophrenia who have OSA.

Other physical disorders

People with psychotic disorders living in Australia have higher rates of virtually all common physical disorders

Key consideration
Regular screening and intervention for cardiometabolic problems in people with schizophrenia should be mandatory, from the first episode of psychosis.

Recommendations relating to physical health of people with psychosis	Type	Level of evidence
Engage the individual and carers in strategies to ensure healthy living (e.g. diet, exercise).	EBR	III-I
If the person is gaining weight or has other metabolic complications of treatment, switch to a weight-neutral antipsychotic agent.	EBR	II
Consider the use of agents such as metformin to reduce weight gain and insulin sensitivity in people taking antipsychotic agents associated with obesity.	EBR	II
Liaise with the GP to ensure optimal treatment for hypertension, elevated cholesterol and other cardiometabolic conditions.	CBR	N/A
For people who do not attend a GP, consider undertaking investigations, monitoring and prescribing as needed to treat physical health problems within the mental health service.	CBR	N/A
Liaise with an endocrinology specialist or other specialist colleagues as appropriate.	EBR	IV
All mental health services should provide evidence-based programmes to address obesity and lack of exercise.	CBR	N/A
All mental health services should provide evidence-based programmes to help smokers to quit.	CBR	N/A
Ensure that regular dental care is provided.	CBR	N/A

GP: general practitioner; EBR: evidence-based recommendation; CBR: consensus-based recommendation.
N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

including chronic pain, headaches, asthma and arthritis (Morgan et al., 2012). They also tend to have poor dental health. Good quality coordination, delivery and monitoring of physical health care are essential.

Section 5. Specific populations and circumstances

Aboriginal and Torres Strait Islander peoples

The Social and Emotional Wellbeing Framework 2004–2009 (Social Health Reference Group for National Aboriginal and Torres Strait Islander Health Council and National Mental Health Working Group, 2004) sets out a holistic approach to the health of Aboriginal and Torres Strait Islander people that is concordant with the cultural and spiritual beliefs of

Australia's first people. This paradigm recognises the complex interplay of factors determining health and mental health outcomes, while acknowledging resilience and strength in the face of adversity.

It is essential for mental health workers who provide care for Aboriginal and Torres Strait Islander people with psychotic illness to appreciate the psychosocial context set out in this framework and important related documents:

- *National strategic framework for Aboriginal and Torres Strait Islander health, 2003–2013* (National Aboriginal and Torres Strait Islander Health Council, 2004).
- *A Contributing Life, the 2012 National Report Card on Mental Health and Suicide Prevention* (National Mental Health Commission, 2012) – acknowledges the historical context of colonisation, dispossession

guide.medlive.cn

and displacement and calls for a more nuanced understanding of the diversity of the Aboriginal and Torres Strait Islander peoples with multiple language groups, cultures and traditions.

- The mental health and social and emotional wellbeing of Aboriginal and Torres Strait Islander peoples, families and communities (Holland et al., 2013) – a supplementary paper to *A Contributing Life*.

There is a lack of comprehensive epidemiological data for Aboriginal and Torres Strait Islander populations for mental health generally and for psychosis specifically (Black et al., 2015). A number of issues have contributed to this lack of research, including methodological issues relating to the need for culturally appropriate tools and research approaches and the diversity of Aboriginal and Torres Strait Islander populations, which makes accurate generalisation difficult (Haswell-Elkins et al., 2007). A study of psychosis in the Indigenous populations of Cape York and the Torres Strait (Hunter et al., 2012) found an overall treated prevalence rate of 1.68%, with higher rates for males than females and higher rates for Aboriginal people than Torres Strait Islander people.

Aboriginal and Torres Strait Islander peoples have disproportionately high rates of suicide, substance use and incarceration. Aboriginal people are hospitalised for mental health and behavioural disorders at around 1.7 times the rate of other Australians (Dudgeon et al., 2014). The prevalence of mental disorder among Indigenous adults in custody across Australia is also likely to be disproportionately high, based on findings in a Queensland prison study (Heffernan et al., 2012). Rates of mental illness among Indigenous people in custody were found to very high compared with community estimates, including rates of psychotic illness of 8% for men and 23% for women.

Social disadvantage is an important contributing factor to mental disorders, including psychosis, in Aboriginal and Torres Strait Islander people (Hunter, 2007). Such disadvantage has a compounding effect on probable rates of psychotic illness, through increased rates of developmental disability and acquired cognitive impairment, secondary to lack of access to antenatal care and to affordable quality nutrition in more remote communities, increased rates of childhood adversity and accidental physical trauma in young people – often complicated by maternal substance abuse and exposure to drug and alcohol use earlier in development.

There is a high burden of physical health problems among Aboriginal and Torres Strait Islander people, even young people (Australian Institute of Health and Welfare [AIHW], 2015), which complicates the management of psychosis. There are increased risks for diabetes, heart disease and renal failure along with psychiatric comorbidities such as depression and substance abuse.

High rates of substance use, particularly in some rural and remote Aboriginal and Islander communities, are likely to contribute to higher rates of psychotic illness or a worsening course of illness, particularly combined with poor access to both community and hospital specialist mental health and drug and alcohol services. Although adequate prevalence data are not available regarding differential prevalence and incidence rates of psychotic illness among Aboriginal and Torres Strait Islander populations within metropolitan, regional, rural and remote communities, rates of psychotic illness are possibly inversely proportionate to community size, which can disproportionately affect smaller communities caring for extended family members living with severe and recurring illness, in settings poor in formal mental health services.

When working with Aboriginal and Torres Strait Islander people, it is important to be aware of the complex interplay of culture, context and clinical significance (Hunter, 2014). 'Symptoms' require particular consideration during assessment and diagnosis especially for somebody who is presenting for the first time with what appears to be psychotic symptomatology. The presence of culturally influenced symptoms similar to psychosis requires careful consideration in diagnosis. Cultural expressions of grief, trauma and loss may be informed by respect for elders and ancestors.

The use of traditional healers, cultural consultants, cultural treatments and Aboriginal health workers can all aid in a clearer formulation and more accurate diagnosis, or serve to provide a culturally informed second opinion. Elders can provide vital cultural insights to the treating team as well as comfort, support, mentoring and advocacy to the individual (Dudgeon et al., 2014). Non-Indigenous clinicians need to accept and incorporate the advice of Indigenous non-clinicians to ensure that schizophrenia is not diagnosed in error or erroneously attributed to cultural factors, and that the subtleties of the interplay between illness and culture are not overlooked.

When designing care plans for Aboriginal and Torres Strait Islander people, the provision of traditional healing treatments and ways, in partnership with mainstream Western medicine, can bring a sense of environmental familiarity and cultural safety, especially if the person is far from home and family. Establishing specialist Indigenous sub-teams within mainstream mental health services has been shown to be a successful model of care (Catts et al., 2013).

Non-Indigenous health professionals may need to modify their communication styles when working with Aboriginal and Torres Strait Islander patients (Dudgeon et al., 2014). All mental health clinicians working in Australia should have mandatory training in Aboriginal and Torres Strait Islander cultural awareness which should include understanding of the following:

- The current relevance of post-colonisation history for Aboriginal and Torres Strait Islander peoples, particularly in regard to collective grief, trauma and loss
- A rights-based approach with particular reference to self-determination and social justice
- Psychosocial determinants of poor mental health in Aboriginal and Torres Strait Islander populations, particularly unstable poor quality accommodation,

guide.medlive.cn

poor access to health care, unemployment, social exclusion, stress, trauma, violence and substance use

- The principles of '*A contributing life*' (National Mental Health Commission, 2012) involving '*thriving not just surviving*', timely and effective care and treatment, meaningful activity and meaningful

connections with family, friends, culture and community.

Although the evidence base is lacking, there are some practice principles that should be implemented in clinical care. The following recommendations are based on

Recommendations on working with Aboriginal and Torres Strait Islander people	Type	Level of evidence
Cultural awareness training should be mandatory for all mental health clinicians.	CBR	N/A
Cultural consultants should be available within mainstream services, ideally matched for gender, language and cultural group.	CBR	N/A
Mainstream health services should create an atmosphere of cultural safety using culturally adapted resources.	CBR	N/A
Mental health services should use engagement strategies that recognise cultural attitudes to mental illness.	CBR	N/A
Consider arranging for a family member or cultural consultant to act as mediator.	CBR	N/A
Adopt an appropriate manner of communication (e.g. narrative 'yarning', a less direct questioning style, open-ended questions).	CBR	N/A
Provide comprehensive treatment, recognising the roles of substance use, stress and trauma in complicating psychosis assessment and management.	CBR	N/A
Carefully share knowledge, to enable informed choices and enhance concordance with treatment.	CBR	N/A
Be aware that antipsychotic medicines may have an increased risk of side effects, especially cardiometabolic syndrome.	CBR	N/A
Be aware that Aboriginal and Torres Strait Islander people with mental illness have an elevated risk of suicide.	CBR	N/A

CBR: consensus-based recommendation.
N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

the current knowledge base and, for the most part, are not specific to schizophrenia or psychosis but reflect a culturally concordant approach.

Māori

Māori mental health is an area of high priority due to the prevalence and pattern of mental health disorders among Māori. There has been an extensive body of work throughout New Zealand exploring various models of care specifically relevant to Māori. These developments include best practice principles that incorporate clinical expertise and cultural competency to enhance services to Māori along with the development of outcome measures that are more appropriate and acceptable to Māori. It is beyond the scope of this guideline to comprehensively review this extensive literature; however, it is imperative that the assessment, treatment and care of Māori who suffer with schizophrenia and their *whānau* (family) are considered within this broader context.

Māori health services. The development of Māori mental health services had a strong foundation in holistic models, such as the Whare Tapa Wha model described by Mason Durie (Durie, 1985), which includes four dimensions of health necessary for Māori wellbeing: spiritual, mental and emotional, physical, and family and community. *Te Wheke* is another framework of health from a Māori perspective, which has existed for many generations and captures eight dimensions of health (Durie, 1998). Kaupapa Māori services are now common throughout New Zealand and are constantly evolving in response to research and the changing needs of Māori. The key principle underpinning these services is culturally appropriate best practice which has been described as the '*synthesis between Indigenous values and the highest international clinical standards*' (Te Rau Matatini and The Werry Centre, 2004). The overall aim of these services is to enhance recovery for Māori who access Mental Health Services by having a service run by Māori for Māori. Kaupapa Māori services operate in the community and in forensic services, inpatient settings and the non-government sector.

guide.medlive.cn

The three principles of a Kaupapa Māori service are:

- *Tino Rangatiratanga* (right to self-determination)
- *He Tangata He Tangata* (recognise the diverse realities of Māori)
- *Tautau Tautau* (collective responsibility of Māori health).

These principles are outlined in *Te ara ahu whakamua: Strategic Directions for Māori: A Discussion Document* (Ministry of Māori Development, 1993). In *Te puawaiwhero*, the second Māori mental health and addiction framework, *whānau ora* (family health) is described as a guiding principle. This acknowledges that mental health for Māori is achieved through maximising the health and wellbeing of the *whānau* (family) (New Zealand Ministry of Health, 2008). A *whānau ora* approach means attending to the health and social needs of the *whānau* of the identified patient. When Māori families are supported to obtain maximum health and wellbeing, this also improves the recovery of the individual.

Providing appropriate care for Māori in mainstream services. Cultural competencies for the non-Māori workforce working with Māori are pivotal to successful service engagement and outcome. Support for the Māori mental health workforce and the appreciation that Māori staff offer a dual competency has been a focus for *Te Rau Matatini* (Baker and Levy, 2013).

Whether Māori are being assessed and treated in Kaupapa Māori services or in mainstream services, it is appropriate that they have access to cultural support and cultural assessment. Often Māori may have already sought advice from *Kaumatua* (elders) or *tohunga* (traditional healers) within their own networks. If this is the case, the person presenting with psychosis and their *whānau* may have excluded cultural or spiritual attributions for their experiences. However, offering the intervention of *Kaumatua* (elders, either from within or external to the service) may be a key component to improved engagement and outcome. The individual and *whānau* may also wish to integrate traditional aspects of health care such as *mirimiri* (massage) or *rongoā* (healing native plants) along with usual clinical care. Optimal recovery is often achieved by synthesising both clinical and traditional approaches.

Culturally appropriate outcome measures have also been developed. *Hua Oranga* (a Māori mental health outcome tool) assesses the effectiveness of mental health treatment and care from the basis of a Māori model of health and uses the perspective of a patient, clinician and *whānau* member (Kingi and Durie, 1999).

Schizophrenia in Māori. Despite the significant importance of this area, research specifically relating to Māori with schizophrenia is limited. In 2003–2005, Māori were over 3.5 times more likely to be hospitalised for schizophrenia than non-Māori. Māori men had a hospitalisation rate for schizophrenia of 416.7 per 100,000 (age standardised to the Māori population) compared with 222.4 for Māori women, 119.7 for non-Māori men and 62.3 per 100,000 for non-Māori women (Robson and Harris, 2007). One-year prevalence of schizophrenia was estimated at 1% for Māori, which was approximately three times that of non-Māori. Māori men had the highest prevalence rates overall of 1.27% in 2002–2003, followed by Māori women (0.7%), non-Māori men (0.41%), then non-Māori women (0.24%) (Kake et al., 2008). Kake (2008) used a capture–recapture method to estimate the population prevalence of schizophrenia. This involved the data from two large data sets recording the diagnosis of people discharged from public and private hospitals and the diagnosis of community mental health patients. This is the first published account of the prevalence of schizophrenia being calculated using this methodology.

Sociocultural factors of relevance for Māori that could contribute to increased risk of schizophrenia include colonisation, poverty and racism (Harris et al., 2006). Māori men have a higher rate and younger onset of cannabis use, which has been identified as an important risk factor for schizophrenia (Gururajan et al., 2012).

Research on Māori and Pakeha (European) people being treated for schizophrenia within clinical services did not demonstrate a difference in attitude towards medication (Sanders et al., 2011). Being aware of the importance of Māori culture should not come with assumptions that Māori will be necessarily opposed to or not interested in information about schizophrenia as a medical condition and the effective treatments available.

Māori have lower life expectancy and higher rates of heart disease and diabetes than Pakeha. They also have higher rates of poverty and cigarette use (New Zealand Ministry of Health, 2008). While a physical health-monitoring programme for people on SGAs is a key part of any mental health service, this needs to be particularly robust for Māori.

Recommendations on working with Māori	Type	Level of evidence
All mental health services and clinicians should provide both clinically and culturally appropriate and informed care for Māori being assessed or treated for schizophrenia.	CBR	N/A
Mental health staff should have access to training in cultural competency for working with Māori with schizophrenia and their *whānau*.	CBR	N/A
The use of *Hua Oranga* as a Māori-specific outcome measure is encouraged.	CBR	N/A

CBR: consensus-based recommendation.
N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

guide.medlive.cn

New Zealand's Pacific Islander peoples

Pacific Islander people living in New Zealand (Pasifika peoples) have higher admission rates to acute mental health units than European people (Nielssen et al., 2013). For the inpatient population, they are three times more likely to have a diagnosis of schizophrenia or a psychotic illness than European people (Gaines et al., 2003).

From the late 1990s, there have been national initiatives to improve the mental health outcomes of Pacific people in New Zealand. Pacific-specific services exist both in the non-government sector and the clinical provider sector. These services provide either direct care to clients or support to general mental health teams. A number of frameworks and models have been developed to assist service delivery for Pacific people. These are specific for Cook Islands, Samoan or Tongan people, but all share the concept of health care integrated with respect for spirituality, roles within the family and community and the use of language (Agnew et al., 2004).

The '*Real skills plus Seitapu*' framework for working with Pacific Peoples recognises the integration of cultural and clinical competencies for staff as an expected standard of care (Te Pou o Te Whakaaro Nui, 2009). Core components of a Pacific mental health service include cultural assessments, use of Pacific language, inviting environments and recognition of spirituality. Assistance with recovery involves having access to culturally and clinically competent staff. Staff also need to be mindful of the importance of stigma for Pacific people with mental illness (Suaalii-Sauni et al., 2009).

Working with a Pacific person who has schizophrenia requires an understanding of family structure, dynamics and roles. Traditionally, Pacific families are extended family groups with the head of the group having responsibility for the wellbeing of all family members. In this case, the leader may make decisions involving the individual's engagement with treatment and also have a role at mobilising supports. Not all Pacific people will be part of such a structure, as the impact of migration has affected families differently. However, developing rapport with the family as well as the client is an essential foundation of a treatment plan.

Understanding the role of language for a Pacific person with schizophrenia includes an awareness of not only verbal but also non-verbal communication. The use of cultural advisors or interpreters enables better rapport building and sharing of information. Another way to build rapport is to observe and demonstrate signs of respect in Pacific culture, for example, taking off shoes before entering a house and using the appropriate Pacific Island greetings.

Traditionally, Pacific people did not consider mental illness to originate from within an individual, but rather as a spiritual possession or the result of a transgression of *tapu* prohibitions. Spirituality for Pacific clients and family may be a blend of traditional, Christian and non-Christian beliefs.

Qualitative research has identified barriers to adherence to antipsychotic medication for Samoan people living in New Zealand (Ioasa-Martin and Moore, 2012). A significant barrier to medication adherence is poverty, which affects the ability to purchase medicines and also affects access to transportation for visits to the doctor or chemist. Another barrier to adherence can occur when family members feel shame about the stigma of mental illness and as a result discourage adherence to antipsychotic medication and related activities such as attending medical appointments and visiting the pharmacist. Additional factors thought to affect poor adherence include the attribution of spiritual causes to mental illness (as noted above) as well as, in some cases, the absence of traditional family support structures.

Recommendations on working with Pacific Islander Peoples	Type	Level of evidence
All mental health clinicians should provide culturally appropriate and informed care for Pacific people being assessed or treated for schizophrenia.	CBR	N/A
Understanding the person within the context of their family and cultural background is essential.	CBR	N/A
Mental health staff should have training in cultural competency in working with Pacific people with schizophrenia and their families.	CBR	N/A

CBR: consensus-based recommendation.
N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

Refugees and culturally and linguistically diverse people. International studies have found that both first- and second-generation migrants are at heightened risk of psychotic disorders (Coid et al., 2008). Visible minority status (related to ethnic group or race) is associated with higher risk. The persistence of risk into the second generation suggests that adverse social factors such as discrimination and social defeat play an important role. However, apart from migrants from Oceania, recent migrants to Australia do not have a greater risk of hospital admission for treatment of psychosis (Nielssen et al., 2013).

Social and cultural factors need to be taken into account in managing schizophrenia in people from refugee backgrounds and culturally and linguistically diverse backgrounds. In particular, cultural beliefs about the causes and treatment of psychotic symptoms will influence the attitude of the person and their family to the illness and to treatment. Refugees and

guide.medlive.cn

migrants have higher rates of substance abuse and post-traumatic stress disorder than the general population, so assessment and treatment of these comorbidities is often needed.

Culture and explanatory models in mental health. Cultural factors will influence presenting features, diagnostic assessment, course and outcome of a range of mental illnesses (Bhui and Bhugra, 2007; Nguyen et al., 2012). Clinicians must be open to the explanatory model used by the person with psychosis. Based on the work of Kleinman and Seeman (2000), this means being open to the way individuals and family members explain, understand or interpret their own or another's mental illness or mental wellbeing. Procter et al. (2014) explain that '*a person's explanatory model will influence the way in which thoughts and experiences are presented, the nature, scope and consequences of distress, behaviour pattern of help seeking, perception of as well as adherence or non-adherence to treatment*' (p. 204). While all consumers make interpretations of their health and wellbeing, cultural explanatory models attempt to understand the deeper meaning structures related to questions such as what something is called and why it started when it did, as well as the severity and likely treatment outcome.

A person's cultural and linguistic background can greatly influence how Western concepts of illness and wellbeing are understood and, therefore, how conditions such as schizophrenia and related disorders should be treated (Procter et al., 2014). For example, in some cultures and religions, conditions like schizophrenia may be attributed to bad karma, spiritual possession or mind–body imbalance. The mind and associated spiritual aspects of being may be viewed as being inseparable from the body, and this can lead to differences in understanding and explaining a mental illness.

For others, there may be even greater challenges when deep inner emotional or spiritual conflicts emerge. This comes into play when certain religious or cultural beliefs or values, which are protective in other circumstances, break down and such events are attributed to the causes of mental illness. People who feel this sense of failure are often reticent to seek help. In other instances, personal hardship may be seen as a way of life with the conditions of mental distress accepted as fate or destiny.

The Framework for Mental Health in Multicultural Australia (2013) highlights the fact that compared with the general community, people from culturally and linguistically diverse communities (including refugees) receive poorer quality mental health care and are more likely to be exposed to adverse safety risks. Cultural awareness questions (Table 9) are designed to help practitioners understand the nature, scope and potential implications of the person's explanatory model (Procter, 2007).

People with Australian Temporary Protection Visas. In December 2014, the Australian Government passed legislation to reintroduce Temporary Protection Visas. These Visas could apply to approximately 30,000 asylum seekers currently living in Australia on Bridging Visas, and to asylum seekers currently held in Immigration Detention Centres on the Australian mainland and on Christmas Island.

Clinicians should be aware of:

- Cultural beliefs that might present as psychotic symptoms, such as belief in demons
- The variability between interpreters, and challenges in using telephone interpreters instead of face-to-face interpreters
- Cultural factors that affect people's trust in authority figures such as doctors and government health services
- The potential call on mental health services to advocate for asylum seekers to remain in Australia
- Challenges in obtaining informed consent from some people with schizophrenia, who are used to deferring treatment decisions to doctors
- The potential to misinterpret symptoms of other conditions, particularly post-traumatic stress disorder, as symptoms of psychosis
- The possible feigning of psychotic symptoms in an attempt to garner support from treating clinicians for asylum seekers to remain in Australia
- The effect on asylum seekers of changes in Government policy regarding such issues as family reunification and obtaining permanent residency.

Table 9. Cultural awareness questions for the assessment of people from refugee and immigrant backgrounds.

Can you tell me about what brought you here? What do you call _____? [*Use the person's words for their problem*]
When do you think it started, and why did it start then?
What are the main problems it is causing you?
What have you done to try and stop/manage _____ to make it go away or make it better?
How would you usually manage _____ in your own culture to make it go away or make it better?
How have you been coping so far with _____?
In your culture, is your _____ considered 'severe'? What is the worst problem _____ could cause you?
What type of help would you be expecting from me/our service?
Are there people in your community who are aware that you have this condition?
What do they think or believe caused _____? Are they doing anything to help you?

Source: Procter (2007).

guide.medlive.cn

Women

Women with schizophrenia experience the illness differently from men (Seeman, 2013b). A tailored approach to the diagnosis and treatment of psychotic disorders in women may improve their outcomes.

Development of schizophrenia in women. Women tend to have a later age of first onset of schizophrenia (Angermeyer and Kühnz, 1988; Eranti et al., 2013), with better premorbid function and better outcomes (Grossman et al., 2006; Walker and Bollini, 2002). Women have been found to experience more paranoid symptoms (Beratis et al., 1994) and to be more likely to appear depressed than men (Morgan et al., 2008). The presence of affective symptoms is linked to more favourable outcomes (Lewine, 2004). Women with schizophrenia tend to have better insight than men (Gómez-de-Regil et al., 2010) which may also lead to a better outcome. Female incidence rates increase more slowly and show a peak between the ages of 15 and 30 years and then a second smaller peak in the 45–50 age group (Castle et al., 1993).

The oestrogen protection hypothesis. The sex differences noted in the age of onset of schizophrenia, in particular the bimodal distribution of the incidence of new schizophrenia cases in women, led researchers to propose that oestrogen may confer protection against the early onset of severe schizophrenia (Häfner et al., 1998; Seeman and Lang, 1990). During the perimenopausal reduction in oestrogen production, women may have a higher risk of developing psychosis for the first time, and women with schizophrenia may have a higher risk of relapse.

Building on evidence for oestrogen having a neuroprotective effect, clinical trials using oestrogen as a treatment adjunct have shown promising results (Kulkarni et al., 2008a, 2014a). More recently, clinical trials conducted with raloxifene (a selective oestrogen receptor modulator) have also shown promising results for women with schizophrenia (Kulkarni et al., 2010). Adjunctive raloxifene treatment improves attention and memory in men and women with schizophrenia (Weickert et al., 2015), adding further evidence to the hypothesis that oestrogen has a neuroprotective effect.

Pregnancy and schizophrenia. Women with schizophrenia are no different to other women in their desire to become parents (Sands, 1995). In the past, however, women with schizophrenia were either actively discouraged or, more likely, their treating clinicians largely ignored the topic. Discussions between women and their doctors rarely include planning pregnancies, since the control of psychosis symptoms often overwhelms the clinical interaction (Kulkarni, 2006). The preferred community-based treatment model provides greater socialisation and hence greater opportunities for sexual relationships. Clearly, there are many psychosocial issues facing pregnant women with

schizophrenia, which clinicians need to address with their female patients (Seeman, 2013a).

Unlike FGAs, some SGAs (e.g. clozapine, quetiapine, aripiprazole) do not increase prolactin, and others (e.g. olanzapine) are less likely to increase prolactin, and hence are less likely to reduce women's fertility. When changing from a drug that increases prolactin to one that does not cause prolactin elevation, clinicians should inform women about this normalisation of their fertility and the potential for unplanned pregnancies, and should discuss contraception (Psychotropic Writing Group, 2013). Risperidone is still associated with some diminution of fertility through its action of elevating release of prolactin by the pituitary gland (Haddad and Wieck, 2004).

Good antenatal care and the safe delivery of a healthy baby are important outcomes. There are two important goals: to ensure that the mother remains well during the pregnancy and the postnatal periods and to ensure that the developing baby does not suffer malformations or developmental problems (Raha et al., 2012).

There is a lack of evidence-based information about the safety of antipsychotic medicines during pregnancy. An evidence-based guideline for antipsychotic prescribing during pregnancy is needed. The Australian National Register of Antipsychotic Medication in Pregnancy (NRAMP) will provide local data towards developing such guidance (Kulkarni et al., 2008b, 2014b). An NRAMP prospective cohort study (Kulkarni et al., 2014b) found that cessation of antipsychotic medication during pregnancy was associated with relapse of psychosis, maternal hospitalisation and the subsequent separation of mother and baby, leading to attachment and bonding problems. A registry similar to NRAMP has been established in Boston in the United States. Results from the Boston sample of 214 live births to women taking SGAs in pregnancy (Cohen et al., 2015) replicate the NRAMP findings that it would be unlikely for SGAs to significantly raise the risk of major malformations beyond that observed in the general population or among control groups using other psychotropic medicines. If women are taking adjunctive mood stabilisers, then the potential teratogenicity of these drugs must also be considered. Sodium valproate is known to be associated with foetal malformation and must be ceased. Lithium can also cause foetal abnormalities but, despite the risk, is occasionally used during pregnancy – expert advice and antenatal care are essential.

Special antenatal care is needed for pregnant women with schizophrenia, particularly those with relapsing, severe illness. Education about nutrition and ceasing smoking, illicit drug use and alcohol intake during pregnancy are important issues for good antenatal care (NHMRC, 2009a). Unfortunately, most health systems do not provide comprehensive, integrated care for pregnant women with schizophrenia. The communication between obstetric services and mental health systems can be minimal, leading to difficult clinical situations and even postpartum relapse of

guide.medlive.cn

psychosis. The management of postpartum psychosis needs a holistic approach with a special focus on keeping mother and baby together. Clinicians should aim to enable the woman to mother her child well because this is critical to optimise the mental health of the next generation.

The safety of antipsychotic agents during breastfeeding is also largely unknown and data are also required about this important area. Most clinicians negotiate the issue of breastfeeding with the new mother. The desire of the new mother to breastfeed her newborn, and to provide the best start in life for her baby, is a strong motivator for breastfeeding. However, there are concerns about antipsychotic drug ingestion by the neonate, and this clinical problem requires data to create evidence-based guidelines.

Women whose first experience of psychosis occurs postpartum require highly specialised care. The classification of postpartum psychosis is still unclear, although the symptoms that most women present with seem to share features of schizoaffective disorder and of bipolar 1 disorder, manic episode. Medication management involves a combination of antipsychotic agents and mood stabilisers such as lithium (Dodd and Berk, 2006; Sharma, 2008). Breastfeeding concerns include drug ingestion by the neonate and sleep deprivation for the mother, which can further exacerbate the illness.

Women with postpartum psychosis, either experiencing psychosis for the first time or presenting with relapse of previous psychosis, require management by a team of clinicians who care for the mother and baby together. There are very few public hospital bed-based services that cater to both the woman and her baby. Specialised mother–baby units are required to provide the best possible care, particularly in view of the need for good bonding between mother and child.

Menopause and women with schizophrenia. Many women with schizophrenia experience a worsening of their mental state at this stage of life, probably due to declining oestrogen levels. Perimenopausal women experience hot flushes, sleep disturbances, mood swings and poor cognitive function, as well as worsening of psychotic symptoms (Soares, 2008). Deterioration in a middle-aged woman's mental state may not be recognised as being due to menopause transition hormone shifts, and treatment involving increased antipsychotic medication, hospitalisations and adding in other psychotropic medicines may only be partially effective.

Hormone Replacement Therapy (HRT) provides an alternative and perhaps more effective approach to the treatment of menopause symptoms, including worsening psychosis. Risks associated with HRT must be considered before prescribing (De Villiers et al., 2013). Good medical care and ongoing monitoring will be needed if HRT is used as a treatment adjunct for menopausal women with schizophrenia. Selective oestrogen receptor modulators, the so-called '*brain oestrogens*' (Nickelsen et al., 1999), may have a role in the augmentation of antipsychotic agents in perimenopausal and postmenopausal women with schizophrenia (Kulkarni et al., 2010).

Other physical health issues associated with the menopause, such as weight gain, hypercholesterolaemia, diabetes, osteoporosis and increased risk of breast cancer, need ongoing medical monitoring. Many of these physical health issues can be exacerbated by antipsychotic medication; hence, there is a greater need for good physical health care and monitoring for women with schizophrenia as they enter the menopause transition (Gupta et al., 2012; Seeman, 2012).

Psychosocial issues related to being middle-aged, such as fears of ageing, loss of fertility, change in domestic situations and other mid-life events, also need assessment and appropriate action by treating clinicians.

Special prescribing considerations. Clinicians need to factor in the sex, weight and ethnicity of their patients in order to prescribe a correct, therapeutic dose of drug with minimal side effects. Because the pharmacokinetics and metabolism of antipsychotic medicines differ between women and men (Seeman, 2009), drug-related adverse effects can occur in women if they are prescribed doses calculated for men. Antipsychotic medicines are sequestered into adipose tissue differently in women, and different liver enzymatic actions can impact on the availability of the drug to the central nervous system (CNS) (Haack et al., 2009; Yonkers et al., 1992).

Gonadal steroid hormones act in the CNS to affect the drug response and are different in men and women (Kulkarni et al., 2008b). Tardive dyskinesia is seen more commonly in women than men (Usall et al., 2007; Yassa and Jeste, 1992). Weight gain is a troubling side effect of many antipsychotic drugs for men and women (Galletly et al., 2012; Haack et al., 2009). A Japanese retrospective investigation of BMI in patients who had been treated with antipsychotic agents over extended periods (Koga, 2003) observed that the risk of weight gain was significantly higher in women than in men (odds ratio 4.94). A review of antipsychotic adverse effects (Seeman, 2009) reported that women experienced worse effects than men in many domains, including weight gain, movement disorders, cardiac arrhythmias and fertility.

Antipsychotic-induced hyperprolactinaemia has been estimated to occur in up to 70% of patients with schizophrenia, depending on the choice of antipsychotic agent (Inder and Castle, 2011). Antipsychotic drugs that cause hyperprolactinaemia pose special problems for women. Prolactin has potent antagonist impact on oestrogen, progesterone and testosterone production. Long-term use of medicines associated with hyperprolactinaemia can cause osteoporosis in both women and men (Dursun et al., 2008; Petty, 1999). Elevated prolactin levels may also be associated with increased risk of developing rapidly progressing breast cancers (Clevenger and Plank, 1997). While a more recent cohort study has not shown an increase in breast cancers in women with serious mental illness (Osborn et al., 2013), it did not report data on the use of medicines associated with hyperprolactinaemia and the duration of treatment of women

with schizophrenia. For good clinical care, it is advisable to recommend breast monitoring and bone density scanning for women older than 50 years who are taking antipsychotic agents that cause hyperprolactinaemia.

Hyperprolactinaemia is also associated with sexual dysfunction, lowered libido, poor vaginal lubrication and anorgasmia. Adding oestrogen or testosterone treatment to the antipsychotic medication may assist these sexual dysfunction problems in postmenopausal and premenopausal women (Davis et al., 2008), but the possible risks of these treatments must be considered. High prolactin levels can also cause anovulatory menstrual cycles and hence infertility.

Psychological treatment for women with schizophrenia. CBT is a useful adjunctive therapy for treatment of persistent symptoms. Specific empowerment issues may need to be addressed (Notman and Nadelson, 2006). Techniques aimed at coming to terms with the illness and the associated losses, and understanding the social context of femininity, are some of the newer approaches that address gender-specific issues.

Cognitive remediation techniques are useful for work skilling programmes for women. Women with longer term schizophrenia may have specific difficulties about entering/re-entering the workforce. It is rare for schizophrenia recovery programmes to focus on parenting skills but for women with schizophrenia who have lost custody of their children due to their illness, this is a key skill which may be needed to be taught in order to regain access to their children. In developing new recovery programmes, the inclusion of mothering skills training should have a high priority. Ongoing support for women with schizophrenia who are caring for children is essential (Campbell et al., 2012).

Service provision for women with schizophrenia. Managing schizophrenia in women requires new approaches that have a clear gender focus. In this way, more specific, better tailored treatments for women with schizophrenia can be developed and implemented to hopefully provide better outcomes for women suffering with the devastating mental illness of schizophrenia.

Over time, the public sector psychiatry wards have come to house more acutely and severely ill patients. In Western countries, most psychiatry wards contain men and women in the same ward setting. Women with schizophrenia can have histories of domestic abuse, and living in mixed gender wards with disinhibited male patients can create situations that may re-traumatise them.

Clinicians have a duty of care to manage their female patients safely and in an environment that promotes recovery. Sexual and other assaults have occurred on inpatient units, and women inpatients experience the majority of such assaults (Johnson, 2006). In 2006, the UK National Patient Safety Agency published a detailed analysis of mental health patient safety incidents that occurred between November 2003 and September 2005, and recommended a policy of gender segregation on psychiatric wards (Johnson, 2006). This is a new trend in psychiatry ward design and will hopefully improve the inpatient treatment experience for women with mental illness.

Key consideration
Ongoing support for mothers with schizophrenia is essential.

Recommendations on caring for women with psychoses	Type	Level of evidence
Adopt a gender-specific, tailored approach to the diagnosis and treatment of psychotic disorders experienced by women.	CBR	N/A
For women who are pregnant or may become pregnant, consider choosing antipsychotic agents that have been associated with fewer foetal adverse effects in available registry data (e.g. olanzapine, quetiapine, risperidone).	EBR	III-3
When managing worsening psychosis in women of perimenopausal age, consider prescribing HRT.	EBR	II
If HRT is used as a treatment adjunct for menopausal women with schizophrenia, provide good medical care and ongoing monitoring.	EBR	II
Drug doses based on female metabolism and physiology should be considered and a regimen should be established to closely monitor side effects.	EBR	III-2
Arrange ongoing breast monitoring and bone density scanning for women who are taking antipsychotic medicines that cause hyperprolactinaemia.	EBR	III-2
Consider adding oestrogen or testosterone treatment to antipsychotic medication to assist sexual dysfunction.	EBR	II
Women with postpartum psychosis should be treated by a team of clinicians who care for the mother and baby together.	CBR	N/A

CBR: consensus-based recommendation; EBR: evidence-based recommendation; HRT: Hormone Replacement Therapy.
N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

guide.medlive.cn

Older people with schizophrenia

Approximately 85% of people with schizophrenia have an onset of illness before age 45, so their experience of ageing is complicated by serious mental illness (McAlpine, 2003). Others experience onset at an older age. There is consensus acceptance of the following diagnostic subtypes (Howard et al., 2000; Rodriguez-Ferrera et al., 2004):

- Late-onset schizophrenia (onset between the ages of 40 and 60 years).
- Very-late onset schizophrenia (onset after the age of 60 years).

Early- and late-onset schizophrenia share the fundamental clinical features of positive symptoms, negative symptoms and functional deficits (Maglione et al., 2014). A higher proportion of women than men experience late-onset illness. Compared with earlier onset, late-onset schizophrenia is associated with less severe positive symptoms and response to lower doses of antipsychotic medications (Maglione et al., 2014; Vahia et al., 2010).

Unmet needs. Older people with schizophrenia have been overlooked in both research and service delivery in favour of younger populations (Cohen et al., 2000; Green et al., 1997). Provision of care for older people with schizophrenia has been characterised by disputes between adult and older adult mental health services over who takes responsibility for coordinating care (McCleery et al., 2008). Older people with schizophrenia prematurely face challenges associated with ageing because of the earlier onset of medical comorbidities and poorer health outcomes. They are at risk of homelessness, inappropriate placement in acute wards, placement in settings primarily designed for management of dementia, poor medical and end-of-life care, or missing out on service provision altogether (McCleery et al., 2008; McGrath and Holewa, 2004). A collaborative approach is needed across service providers, including general adult and older adult mental health services, as well as multidisciplinary teams (including aged care assessors, geriatric medical and palliative care teams).

Outcomes for older people with schizophrenia. Evidence from studies reporting outcomes for people with schizophrenia in later life is limited, but suggests that older people with schizophrenia remain symptomatic and impaired, with full recovery being rare (Auslander and Jeste, 2004; Jeste et al., 2003). Cognitive impairment has a greater impact on function in daily living than the continued presence of positive and negative symptoms (Twamley et al., 2002).

There is no evidence of an increased incidence of Alzheimer's disease in older people with schizophrenia, compared with the general population. It has been speculated that the progression of cognitive impairment in schizophrenia might be explained by the concept of decreased cognitive reserve, in which the impact of ageing on the brain is accentuated (Arnold, 2001; Arnold et al., 1998).

Older people with schizophrenia have elevated rates of cardiovascular, respiratory, gastrointestinal, neurological and endocrine diseases, leading to increased mortality and morbidity (Goff et al., 2005), and are more likely than the general population to have unhealthy lifestyle factors. Despite this, older people with schizophrenia are less likely to receive assistance with health interventions such as support with smoking cessation, less likely to obtain correctional hearing and visual aids and are overall less likely to receive best quality medical care (Druss et al., 2001). There has been very little research addressing the issue of end-of-life care for people with mental illnesses, but this population is disadvantaged in accessing quality palliative care (McGrath and Holewa, 2004).

Pharmacological treatments. On average, people with late-onset and very-late-onset schizophrenia respond to much lower doses of antipsychotic medicines than people with early-onset schizophrenia; doses may be reduced by half in the management of late-onset schizophrenia and by as much as 10 times lower in the management of very-late-onset schizophrenia (Howard et al., 2000).

Older people are more susceptible to side effects from antipsychotic medicines. There is an increased risk of death associated with the use of antipsychotics in older people, particularly in people with comorbid dementia (Maust et al., 2015). Older people are more sensitive to anticholinergic side effects, and psychotropic medicines may increase vulnerability to delirium. The metabolic side effects of antipsychotic medicines are particularly relevant. While some older people may receive benefit from clozapine, there is increased risk of clozapine-induced agranulocytosis (Essali et al., 2009). The incidence of tardive dyskinesia in people treated with antipsychotic medications has been found to be 60% in people aged over 65 years and as high as 93% in people aged over 75 years (Byne et al., 1998; Quinn et al., 2001). A correlation between tardive dyskinesia and cognitive impairment has been found (Quinn et al., 2001; Waddington, 1995).

Psychological and psychosocial therapies. Older people with schizophrenia may benefit from a range of psychological and psychosocial therapies. For instance, cognitive behavioural-based social skills training has been shown to improve coping, self-management of symptoms and social functioning (Granholm et al., 2005). Other therapies such as animal-assisted therapies have shown benefit (Barak et al., 2001).

Lifestyle and accommodation support. A wide range of accommodation options is required, ranging from appropriately supported independent community living to high-level care and residential aged care accommodation. Older

people with schizophrenia are at risk of being placed in aged care environments that are primarily designed for dementia care, which have marked disadvantages for people with schizophrenia due to their different clinical needs (McCleery et al., 2008).

Coordinated service provision. Discussion of service provision for older people with schizophrenia has focussed on whether people growing older with early-onset schizophrenia should continue to receive services provided by general adult services or transition to services for older adults. Continuing with adult services may provide important continuity for individuals who have established relationships with care providers. Nevertheless, services for older adults may have more developed skills and knowledge relating to managing comorbid cognitive and medical issues associated with ageing and may have improved access to services for older people experiencing frailty and decreasing function. It is increasingly acknowledged that entry points to mental health services for older people should be determined by assessment of individual needs rather than age of onset of illness or previous relationship with an adult service (McCleery et al., 2008).

Key consideration
A care-coordination model, identifying a leading agency and facilitating input from a broad multidisciplinary team, is an effective model for providing care for older people with schizophrenia.

Recommendations on services for older people with schizophrenia	Type	Level of evidence
Streamlined, accessible, high-quality medical and physical health care services should be made available for older people with schizophrenia.	CBR	N/A
Health care for older people with schizophrenia should be provided by multidisciplinary teams coordinated by a service that is identified as the leading agency. The choice of whether care is provided by a general adult mental health team or a specialised older age mental health team should be based on the individual's needs, not solely on age and previous service provision.	EBR	I
Older people with schizophrenia should have a full range of psychological therapies and psychosocial interventions available to them.	CBR	N/A
Older people with schizophrenia should be provided a range of accommodation options with appropriate levels of support, ranging from independent living to quality residential aged care environments.	CBR	N/A
Antipsychotic medicines should be down-titrated to the lowest effective dose when treating older people with schizophrenia, who are more susceptible to adverse side effects than younger people.	EBR	III-2
Prescribers should be aware of the effects of polypharmacy when prescribing for older people with schizophrenia, and minimise the potential for adverse pharmacokinetic interactions.	EBR	III-2
Older people with schizophrenia should be supported to develop advanced care directives in order to articulate their preferences for all aspects of care as they age through to the end of life.	CBR	N/A
Focussed research investigating the needs of older people with schizophrenia and developing effective interventions in care should be initiated and funded to improve outcomes for this population.	CBR	N/A

CBR: consensus-based recommendation; EBR: evidence-based recommendation.
N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

Schizophrenia in forensic settings

Studies of mental disorder among prisoners consistently show that about 5% of prisoners have a diagnosis of schizophrenia (Nielssen and Misrachi, 2005). The rate of psychotic disorder appears to be even higher among Aboriginal and Torres Strait Islander people in prison, especially females (Heffernan et al., 2012). Prison is often a suboptimal setting to treat mental illness because of the loss of continuity of care through the frequent movement of prisoners between prisons and in and out of custody, and because the environment in prisons can be threatening and counter-therapeutic.

Schizophrenia is associated with an increased rate of recidivism and re-imprisonment (Fazel and Yu, 2011). Comorbid substance use and non-adherence to treatment are major factors contributing to the higher rate of imprisonment of people with schizophrenia (Yee et al., 2011) and also

guide.medlive.cn

higher rates of recidivism after release (Fazel et al., 2014). Persistent aggression despite adequate treatment presents a challenge for both forensic and community mental health services, and may warrant a trial of treatment with clozapine, which is reported to reduce aggression and self-harm, even when there is no appreciable reduction in positive symptoms (Frogley et al., 2012).

The interface between prison and community services is often poorly managed. Prisoners released from remote low-security prisons are often distant from their family and friends and from the services likely to be involved in their ongoing care. When there is uncertainty about a released prisoner's address, it is unclear which service will be responsible for providing care. Staff of community services can be anxious about engaging with people with a history of violence and offending. Finally, there is often a lack of coordination between parole and mental health services.

Recommendations on the management of psychosis in forensic settings	Type	Level of evidence
The standard of care offered to prisoners with schizophrenia should be equal to that available in the community.	CBR	N/A
Where possible, people with acute episodes of mental illness should be treated in a hospital or a therapeutic area free from threat.	CBR	N/A
Particular attention should be paid to continuity of care for people with schizophrenia, both within the prison system and at the time of their release.	CBR	N/A
Post-release treatment plans should be prepared well before people with schizophrenia in prison are eligible for release.	CBR	N/A
The effective treatment of comorbid substance use might reduce the rate of re-offending.	EBR	I
A trial of clozapine may be indicated for people with persistent aggression despite adequate treatment.	EBR	II

CBR: consensus-based recommendation; EBR: evidence-based recommendation.
N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

Section 6. Other considerations

Housing and homelessness

The poverty and social disability associated with schizophrenia affect the ability to obtain and keep accommodation. As many as one-third of the homeless people in our cities have schizophrenia (Teesson et al., 2004). Moreover, the lack of stable housing has an adverse effect on continuity of care and recovery from episodes of illness. The lack of suitable housing also has an adverse effect on the mental health system, as many hospital beds are occupied by people who cannot be discharged because they do not have suitable accommodation. Improving housing improves many health indicators. The literature clearly supports the '*housing first*' approach (Chilvers et al., 2006). The level of support needs to be tailored to the social skills and deficits of each individual.

Many people with schizophrenia live with parents or other relatives. The next most common model is public housing, in the form of subsidised single-person dwellings. A third model is private boarding house accommodation, either renting a room or with the addition of meals and supervised medication. A fourth model is purpose built shared accommodation, with a cluster of individual units set around shared facilities, with either a caretaker or concierge monitoring access or support staff providing assistance during the day. There is a clear need for more services in residential settings, including support for family members caring for a person with schizophrenia at home, supervision of adherence to medication, protection from exploitation and assistance to overcome deficits in social skills (e.g. financial management, cleaning and food preparation).

Treatment of people with schizophrenia who are homeless or choose to live in the open presents particular challenges. Common reasons for homelessness include the choice to save money for substance use, as well as the presence of persecutory beliefs involving services and institutions. The challenge

Recommendations on psychosocial considerations	Type	Level of evidence
Health services should advocate for the development of a range of models of supported accommodation.	CBR	N/A
An occupational therapy assessment, to establish an individual's capacity for independent living and support requirements, should be available where indicated.	EBR	I

CBR: consensus-based recommendation; EBR: evidence-based recommendation.
N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

guide.medlive.cn

is to design services that can attract and serve this group and persuade them to accept more secure forms of housing.

Comorbid psychiatric conditions

Prevalence and risk factors. People with schizophrenia suffer from high rates of psychiatric comorbidities, including depression and anxiety disorders (Buckley et al., 2009). The lifetime modal rate for major depression in schizophrenia has been estimated at 25%, while rates of depression not meeting major depression criteria are very much higher (Siris, 2000). Overall, lifetime rates of 10–12% for generalised anxiety disorder, 4–20% for panic disorder, 5–20% for agoraphobia and 30% for social anxiety disorder have been reported in people with schizophrenia (Pokos and Castle, 2006). Obsessive compulsive disorder (OCD) appears to become more common as schizophrenia progresses, such that around 11–15% of people with early-onset schizophrenia might manifest the disorder, growing to 22–30% later in the course of the illness (Pokos and Castle, 2006).

Antipsychotic agents with antiserotonergic properties (notably clozapine and olanzapine) can be associated with exacerbation or de novo presentation of OCD (Schirmbeck et al., 2011). Psychiatric comorbidities are often undertreated due to several factors:

- The prevailing hierarchical approach to psychiatric diagnoses can lead to clinicians labelling all behaviours and symptoms as part of the schizophrenia syndrome (e.g. assuming social withdrawal is due to negative symptoms rather than other factors such as social anxiety disorder).
- Clinicians may fail to ask requisite questions to disentangle core psychotic symptoms from depressive and anxiety symptoms.
- Clinicians may believe that psychological and pharmacological treatments for depression and anxiety disorders will not be effective in people with schizophrenia.

Management. There is little evidence to guide the management of comorbid psychiatric conditions in people with schizophrenia. Most studies have focussed on depression and have evaluated pharmacological treatments.

Comorbid depression. Antidepressant medicines appear to be only slightly effective for managing comorbid major depression in people with schizophrenia (Castle and Bosanac, 2012). The potential for drug–drug interactions and additional side effects should be considered before prescribing antidepressants in people already taking psychotropic medicines (Castle and Bosanac, 2012). For example, akathisia can be worsened by selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs), and weight gain and sedation can be exacerbated by mirtazapine.

It has been suggested that treatment with antidepressants be deferred in the acute phase of psychosis as symptoms may resolve as the psychosis settles, and that some antidepressants may exacerbate psychotic symptoms (Siris, 2000). There is controversy as to whether the SGAs have inherent antidepressant effects in schizophrenia (Castle and Bosanac, 2012). A specific effect of clozapine in reducing suicidality in people with schizophrenia has been demonstrated (Hennen and Baldessarini, 2005; Meltzer et al., 2003).

Psychological approaches have not been widely employed to target depression in schizophrenia. A number of studies using CBT, which have effectively targeted residual psychotic symptoms in schizophrenia, have reported associated improvements in depressive symptoms (Pilling et al., 2002). Social isolation, stigma and family stress are obvious targets for intervention in the depressed person with schizophrenia. The concepts of demoralisation (Clarke and Kissane, 2002) and social defeat (Selten et al., 2013) can assist in understanding the subjective experiences of many people with schizophrenia, especially those with depressive symptoms that may not qualify for a diagnosis of comorbid major depressive disorder. However, very few studies have evaluated the effects of social interventions.

Comorbid anxiety disorders. There is even less evidence to guide the management of anxiety disorders than depression in people with schizophrenia. Very few studies have evaluated treatments for comorbid anxiety disorders in people with schizophrenia. Anxiety symptoms often predominate in the prodromal period. In addition, many people with schizophrenia and related disorders experience symptoms of anxiety without necessarily meeting full criteria for an anxiety disorder.

In the absence of specific guidelines for managing comorbid anxiety disorders in people with schizophrenia, clinicians usually follow general treatment guidelines for anxiety disorders. While this seems a reasonable approach, standard approaches to the treatment of anxiety disorders in non-psychotic people have not been evaluated for people with schizophrenia. Potential adverse effects include drug–drug interactions (e.g. fluvoxamine increasing serum levels of clozapine) and cumulative side effect burden (e.g. sexual side effects with SSRIs and antipsychotics).

Psychological strategies might also need to be modified (e.g. by linking inter-session homework for social anxiety in schizophrenia to case-manager-aided exposure response prevention exercises) (Halperin et al., 2000; Kingsep et al., 2003).

Recommendations on managing comorbid conditions	Type	Level of evidence
People with schizophrenia should be screened regularly for mood and anxiety symptoms.	EBR	III-2
Consider mood and anxiety disorders in the differential diagnosis of negative symptoms.	EBR	III-3
In the acute phase of psychosis, treat the psychotic symptoms as the priority, as depressive and anxiety symptoms often settle.	EBR	IV
If depressive and anxiety symptoms persist, ensure organic causes (including drugs and alcohol) are assessed and adequately managed. Consider the possibility that these symptoms may be due to impending relapse.	EBR	III-3
If depressive and anxiety symptoms persist and are not due to organic factors, employ appropriate psychological treatments.	EBR	II
If depressive symptoms or anxiety symptoms do not respond adequately to psychological interventions, consider switching to an antipsychotic agent that has been associated with improvement in these symptoms.	EBR	II
If depressive or anxiety symptoms persist despite optimisation of antipsychotic treatment, consider adding an antidepressant or anxiolytic agent.	EBR	II
Avoid using additional agents that have pharmacokinetic interactions with the antipsychotic agent.	EBR	IV
Choose additional agents that are least likely to exacerbate the side effects associated with the antipsychotic agent.	EBR	IV

EBR: evidence-based recommendation.

Trauma

Exposure to adversity in childhood, including physical, sexual and emotional abuse, neglect, parental death and bullying, is associated with almost a three-fold risk of developing a psychotic illness (Varese et al., 2012). Unsurprisingly, people with schizophrenia have high rates of comorbid post-traumatic stress disorder as well as other comorbidities known to be associated with childhood adversity, such as depression, anxiety and substance use disorders (Achim et al., 2011). In addition, the experience of psychosis can also cause post-traumatic symptoms.

Clinicians often avoid asking people with schizophrenia about exposure to adversity (Lommen and Restifo, 2009; Read et al., 2005). Perceived lack of knowledge and training, concern about deterioration and poor engagement and lack of institutional support have all been identified as barriers preventing treatment of post-traumatic symptoms in people with psychosis (Gairns et al., 2015). As part of the assessment of a person with psychosis, clinicians should ask about exposure to adversity, as this has a bearing on the clinical presentation, illness course and treatment.

Further research is needed to determine the best treatments for post-traumatic symptoms in people with schizophrenia. Psychoeducation and cognitive and behavioural strategies to reduce anxiety may be helpful (Frueh et al., 2009; Mueser et al., 2008). Exposure therapy and other specific therapies to address post-traumatic stress disorder in people with schizophrenia require further research before they can be recommended as treatments for schizophrenia. As trauma exposure and its sequelae are so common in those with schizophrenia, this should be a research priority.

Key consideration
Clinicians should ask people with schizophrenia about exposure to trauma, including maltreatment and adversity in childhood and traumatic experiences in adult life.

Recommendations relating to trauma	Type	Level of evidence
Clinicians should take a history of trauma into consideration when organising care, such as choosing the gender of the therapist, and when facing challenges in establishing a trusting therapeutic alliance.	CBR	N/A
Clinicians should be mindful that exposure to trauma is associated with an increased likelihood of symptoms of depression and anxiety.	CBR	N/A

CBR: consensus-based recommendation.
N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

guide.medlive.cn

Violence, suicide and victimisation

Suicide is a significant cause of premature mortality in schizophrenia, and 5–6% of people with a diagnosis of schizophrenia end their lives by suicide (Hor and Taylor, 2010; Palmer et al., 2005). The risk of suicide and self-harm appears to be greatest prior to initial treatment and in the period immediately after initial treatment (Challis et al., 2013), but continues throughout life. The main risk factors for suicide in schizophrenia are the same as those identified in people with other psychiatric disorders, and include male sex, previous suicide attempts, depressed mood and substance use (Hor and Taylor, 2010). Lopez-Morinigo et al. (2012) found that there is little evidence that insight is a risk factor for suicide in people with schizophrenia.

Although most people with schizophrenia will never commit an act of violence, people with schizophrenia are over-represented among perpetrators of violence, especially serious violence. For example, meta-analysis has shown that worldwide, 6.5% of homicide offenders have schizophrenia (Large et al., 2009) compared to the community prevalence of schizophrenia of 0.44% (McGrath et al., 2004). The most common reasons for violence are the presence of frightening symptoms, comorbid substance abuse (which has negative impacts on lifestyle and self-control) and the loss of continuity of care.

The routine use of risk-assessment instruments is likely to be of little value in predicting which person with schizophrenia will go on to commit serious violence, because of the low rate of serious violence, the lack of specific risk factors associated with acts of violence and the influence of an individual's particular circumstances on the timing of acts of violence (Large et al., 2011b). However, some acts of violence might be prevented by the universal precautions of treating FEP earlier, assertive treatment of comorbid substance use and providing urgent assessment and treatment to people presenting with symptoms in which they believe they are in danger.

People with psychotic disorders are also more likely to be victims of violence. Morgan et al. (2015) found that compared to the population rate of 3.4% per year, people with psychosis are 4.8 times more likely to be the victim of a violent offence. Reasons for the increased rate of being assaulted include poverty and living in deprived areas with higher rates of violence, living in the open, the increased risk of assault in custodial settings and the effect of alarming behaviour associated with untreated illness (Maniglio, 2009). However, the key predictor of a person with schizophrenia being the victim of violence is comorbid substance abuse (Dolan et al., 2012).

Key considerations
Early treatment of first-episode psychosis may prevent some acts of violence and self-harm.
Reducing comorbid substance use can also reduce violence and other offending.

Recommendations on managing vulnerability, violence and self-harm	Type	Level of evidence
Ensure that people with the delusional belief that they are in danger receive urgent treatment, including involuntary hospital admission if necessary.	EBR	IV
Providing supported accommodation in which people with schizophrenia are protected from intimidation might reduce the risk of being the victim of violence.	CBR	N/A
Treating substance use disorder can reduce the likelihood of people with schizophrenia becoming the victims of violence.	CBR	N/A

EBR: evidence-based recommendation; CBR: consensus-based recommendation.
N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

Research and evaluation

Clinical measurement. Much of the treatment of people with schizophrenia involves heuristic decision-making that is based on the clinical experience of the person providing the care, and is not informed by any objective measurement of the results of changes in treatment. This is of particular concern for consistency of treatment when doctors change regularly (e.g. for people with long-term schizophrenia treated at community facilities by trainee psychiatrists, who rotate every few months). Moreover, the lack of experience or any developed habit of clinical measurement affects trainee psychiatrists' ability to critically evaluate research based on commonly used instruments. Medical records are full of risk-assessment instruments, but contain very little in the way of clinical measurement. Ideally, all doctors treating people with schizophrenia would routinely use scales for measurement of symptoms, including positive, negative and depressive symptoms, as well as side effects of treatment and cognitive and social performance. Widely

guide.medlive.cn

Recommendations for further research and evaluation	Type	Level of evidence
Use validated instruments to record clinical signs, side effects and response to treatment, where possible.	CBR	N/A
Trainee psychiatrists should be trained in the selection, administration, scoring and interpretation of the instruments used in psychiatric research and clinical practice.	CBR	N/A
Mental health services should routinely measure service performance, including duration of untreated psychosis, duration to second admission, measures of adherence to treatment, patient involvement in care and patient satisfaction with treatment.	CBR	N/A

CBR: consensus-based recommendation.

N/A: Level of evidence category does not apply; recommendation based on a combination of available evidence, clinical experience and expert consensus.

used scales that might improve the objective measurement of symptoms and side effects include the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) and the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976) for side effects. Trainee psychiatrists should be familiar with the items in the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987) which forms the basis of assessing the efficacy of antipsychotic medication. Depression can be assessed using the Calgary Depression Scale for Schizophrenia (CDS) (Addington et al., 1992), the Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) or the Beck Depression Inventory (Beck et al., 1961).

Cognition is not a unitary concept and there is no universal cognition scale that would be reliable and valid in any routine clinical assessment. The tool that is close to a practicable clinical assessment of cognitive functions is the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph et al., 1998). The use of the RBANS by non-psychologists requires a brief supervised training that can be provided by a neuropsychologist. Another option is the Brief Cognitive Assessment Tool for Schizophrenia (B-CATS; Hurford et al., 2011) which has not been widely validated but is made up of three tests selected from more comprehensive neuropsychological batteries. The Brief Cognitive Assessment (BCA; Velligan et al., 2004) is a brief battery designed to measure changes in cognition. See also *'Cognitive function' in 'Section 3. Treatment: context, structure and content of interventions'*.

There are numerous measures of social function used in research, but most are too long to be practical for clinical use. The Daily Activity Report (DAR) takes a new approach, measuring functional outcome by recording a person's daily activity for 7 days, based on phone calls made three times a day (Velligan et al., 2015).

There is also a need for services to record information that allows the comparison of performance of services and the performance of a service over time, including measures of duration of untreated psychosis, duration from first contact to treatment, rates of seclusion, absconding, use of involuntary treatment, continuity of care, duration to first relapse, reliability of clinical communication and particularly measures of

the individual's participation in their treatment planning and their satisfaction with the care that they are receiving.

Disclaimer

Compiled for the Royal Australian and New Zealand College of Psychiatrists (RANZCP), this information and advice is based on current medical knowledge and practice as at the date of publication. This clinical practice guideline is intended as a general guide

guide.medlive.cn

only, not as a substitute for individual medical advice. The RANZCP and its employees accept no responsibility for any consequences arising from relying upon the information contained in this publication.

References

Abraham KR and Kulhara P (1987) The efficacy of electroconvulsive therapy in the treatment of schizophrenia: A comparative study. *The British Journal of Psychiatry* 151: 152–155.

Achim A, Maziade M, Raymond E, et al. (2011) How prevalent are anxiety disorders in schizophrenia? A meta-analysis and critical review on a significant association. *Schizophrenia Bulletin* 37: 811–821.

Addington D, Addington J, Maticka-Tyndale E, et al. (1992) Reliability and validity of a depression rating scale for schizophrenics. *Schizophrenia Research* 6: 201–208.

Adolphs R (2001) The neurobiology of social cognition. *Current Opinion in Neurobiology* 11: 231–239.

Agnew F, Pulotu-Endemann FK, Robinson G, et al. (2004) *Pacific Models of Mental Health Service Delivery in New Zealand ('PMMHSD') Project*. Auckland, New Zealand: Health Research Council of New Zealand.

Al Lawati NM, Patel SR and Ayas NT (2009) Epidemiology, risk factors, and consequences of obstructive sleep apnea and short sleep duration. *Progress in Cardiovascular Diseases* 51: 285–293.

Aleman A, Kahn RS and Selten JP (2003) Sex differences in the risk of schizophrenia: Evidence from meta-analysis. *Archives of General Psychiatry* 60: 565–571.

Allen MH, Debanne M, Lazignac C, et al. (2011) Effect of nicotine replacement therapy on agitation in smokers with schizophrenia: A double-blind, randomized, placebo-controlled study. *The American Journal of Psychiatry* 168: 395–399.

Álvarez-Jiménez M, Gleeson JF, Henry LP, et al. (2012a) Road to full recovery: Longitudinal relationship between symptomatic remission and psychosocial recovery in first-episode psychosis over 7.5 years. *Psychological Medicine* 42: 595–606.

Álvarez-Jiménez M, González-Blanch C, Vázquez-Barquero JL, et al. (2006) Attenuation of antipsychotic-induced weight gain with early behavioral intervention in drug-naive first-episode psychosis patients: A randomized controlled trial. *Journal of Clinical Psychiatry* 67: 1253–1260.

Álvarez-Jiménez M, Priede A, Hetrick SE, et al. (2012b) Risk factors for relapse following treatment for first episode psychosis: A systematic review and meta-analysis of longitudinal studies. *Schizophrenia Research* 139: 116–128.

American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition. Arlington, VA: American Psychiatric Publishing.

Amminger GP, Schäfer MR, Papageorgiou K, et al. (2010) Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: A randomized, placebo-controlled trial. *Archives of General Psychiatry* 67: 146–154.

Andreasen NC, Carpenter WT, Kane JM, et al. (2005) Remission in schizophrenia: Proposed criteria and rationale for consensus. *The American Journal of Psychiatry* 162: 441–449.

Angermeyer M and Kühnz L (1988) Gender differences in age at onset of Schizophrenia. *European Archives of Psychiatry and Neurological Sciences* 237: 351–364.

Anthony WA. (1993) Recovery from mental illness: The guiding vision of the mental health service system in the 1990s. *Psychiatric Rehabilitation Journal* 16: 11–23.

Arango C, Garibaldi G and Marder SR (2013) Pharmacological approaches to treating negative symptoms: A review of clinical trials. *Schizophrenia Research* 150: 346–352.

Arnold SE (2001) Contributions of neuropathology to understanding schizophrenia in late life. *Harvard Review of Psychiatry* 9: 69–76.

Arnold SE, Trojanowski JQ, Gur RE, et al. (1998) Absence of neurodegeneration and neural injury in the cerebral cortex in a sample of elderly patients with schizophrenia. *Archives of General Psychiatry* 55: 225–232.

Ashton M, Mulconray S, Weston M, et al. (2013) Peer workers' role in smoking-cessation groups for people with mental illness. *Australasian Psychiatry* 21: 246–248.

Ashton M, Rigby A and Galletly C (2015) Evaluation of a community-based smoking cessation programme for people with severe mental illness. *Tobacco Control* 24: 275–280.

Auslander LA and Jeste DV (2004) Sustained remission of schizophrenia among community-dwelling older outpatients. *The American Journal of Psychiatry* 161: 1490–1493.

Australian Government Department of Health (2009) Fourth national mental health plan: An agenda for collaborative government action in mental health 2009–2014. Available at: www.health.gov.au/internet/main/publishing.nsf/%20content/mental-pubs-f-plan09 (accessed 16 March 2016).

Australian Government Therapeutic Goods Administration (2014) *Australian Public Assessment Report for Lurasidone Hydrochloride*. Canberra, ACT, Australia: TGA.

Australian Health Ministers' Advisory Council (2013) *A National Framework for Recovery-Oriented Mental Health Services: Guide for Practitioners and Providers*. Canberra, ACT, Australia: Australian Government Department of Health and Ageing.

Australian Institute of Health and Welfare (AIHW) (2015) *The Health and Welfare of Australia's Aboriginal and Torres Strait Islander Peoples 2015* (Cat. no. IHW 147). Canberra, ACT, Australia: AIHW.

Bak M, Fransen A, Janssen J, et al. (2014) Almost all antipsychotics result in weight gain: A meta-analysis. *PLoS ONE* 9: e94112.

Baker AL, Richmond R, Kay-Lambkin FJ, et al. (2015) Randomized controlled trial of a healthy lifestyle intervention among smokers with psychotic disorders. *Nicotine and Tobacco Research* 17: 946–954.

Baker M and Levy M (2013) E Toru Ngā Mea. *Pimatisiwin: A Journal of Aboriginal and Indigenous Community Health* 11: 471.

Balzan RP, Delfabbro PH, Galletly CA, et al. (2014) Metacognitive training for patients with schizophrenia: Preliminary evidence for a targeted, single-module programme. *Australian and New Zealand Journal of Psychiatry* 48: 1126–1136.

Barak Y, Savorai O, Mavashev S, et al. (2001) Animal-assisted therapy for elderly schizophrenic patients: A one-year controlled trial. *The American Journal of Geriatric Psychiatry* 9: 439–442.

Barnes CW, Alderton D and Castle D (2002). The development of clinical guidelines for the use of Zuclopenthixol acetate. *Australasian Psychiatry* 10: 54–58.

Beck AT, Ward CH, Mendelson M, et al. (1961) An inventory for measuring depression. *Archives of General Psychiatry* 4: 561–571.

Bennett ME, Wilson AL, Genderson M, et al. (2013) Smoking cessation in people with schizophrenia. *Current Drug Abuse Reviews* 6: 180–190.

Beratis S, Gabriel J and Hoidas S (1994) Age at onset in subtypes of schizophrenic disorders. *Schizophrenia Bulletin* 20: 287–296.

Berk M, Copolov D, Dean O, et al. (2008) *N*-acetyl cysteine as a glutathione precursor for schizophrenia – A double-blind, randomized, placebo-controlled trial. *Biological Psychiatry* 64: 361–368.

Bertelsen M, Jeppesen P, Petersen L, et al. (2008) Five-year follow-up of a randomized multicenter trial of intensive early intervention vs stand-

guide.medlive.cn

ard treatment for patients with a first episode of psychotic illness: The OPUS trial. *Archives of General Psychiatry* 65: 762–771.

Bhui K and Bhugra D (2007) *Culture and Mental Health: A Comprehensive Textbook*. London: Hodder Arnold.

Birchwood M and Fiorillo A (2000) The critical period for early intervention. *Psychiatric Rehabilitation Skills* 4: 182–198.

Black EB, Ranmuthugala G, Kondalsamy-Chennakesavan S, et al. (2015) A systematic review: Identifying the prevalence rates of psychiatric disorder in Australia's Indigenous populations. *Australian and New Zealand Journal of Psychiatry* 49: 412–429.

Bond GR, Drake RE and Becker DR (2012) Generalizability of the Individual Placement and Support (IPS) model of supported employment outside the US. *World Psychiatry* 11: 32–39.

Bosanac P and Castle DJ (2015) Why are long-acting injectable antipsychotics still underused? *Advances in Psychiatric Treatment* 21: 98–105.

Bourque F, van der Ven E and Malla A (2011) A meta-analysis of the risk for psychotic disorders among first- and second-generation immigrants. *Psychological Medicine* 41: 897–910.

Bowie CR, Leung WW, Reichenberg A, et al. (2008) Predicting schizophrenia patients' real-world behavior with specific neuropsychological and functional capacity measures. *Biological Psychiatry* 63: 505–511.

Braga RJ and Petrides G (2005) The combined use of electroconvulsive therapy and antipsychotics in patients with schizophrenia. *The Journal of ECT* 21: 75–83.

Brandon S, Cowley P, McDonald C, et al. (1985) Leicester ECT trial: Results in schizophrenia. *The British Journal of Psychiatry* 146: 177–183.

Brunelin J, Mondino M, Gassab L, et al. (2012) Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. *The American Journal of Psychiatry* 169: 719–724.

Brunette MF and Mueser KT (2006) Psychosocial interventions for the long-term management of patients with severe mental illness and co-occurring substance use disorder. *Journal of Clinical Psychiatry* 67(Suppl. 7): 10–17.

Buckley PF, Miller BJ, Lehrer DS, et al. (2009) Psychiatric comorbidities and schizophrenia. *Schizophrenia Bulletin* 35: 383–402.

Byne W, White L, Parella M, et al. (1998) Tardive dyskinesia in a chronically institutionalized population of elderly schizophrenic patients: Prevalence and association with cognitive impairment. *International Journal of Geriatric Psychiatry* 13: 473–479.

Campbell L, Hanlon M-C, Poon AWC, et al. (2012) The experiences of Australian parents with psychosis: The second Australian national survey of psychosis. *Australian and New Zealand Journal of Psychiatry* 46: 890–900.

Cantor-Graae E and Selten JP (2005) Schizophrenia and migration: A meta-analysis and review. *The American Journal of Psychiatry* 162: 12–24.

Cardinal RN and Bullmore ET (2011) *The Diagnosis of Psychosis*. Cambridge: Cambridge University Press.

Castle D and Bosanac P (2012) Depression and schizophrenia. *Advances in Psychiatric Treatment* 18: 280–288.

Castle DJ and Buckley PF (2015) *Schizophrenia*, 2nd Edition. Oxford: Oxford University Press.

Castle DJ, Tran N, Bosanac P and Alderton D (2012) Management of acute behavioural disturbance in psychosis. In: Castle DJ, Copolov DL, Wykes T and Mueser K (eds.) *Pharmacological and Psychosocial Treatments in Schizophrenia*, 3rd Ed. London: Informa Healthcare. pp. 119–136.

Castle DJ, Wessely S and Murray RM (1993) Sex and schizophrenia: Effects of diagnostic stringency, and associations with and premorbid variables. *The British Journal of Psychiatry* 162: 658–664.

Catts S, O'Toole B, Neil A, et al. (2013) Best practice in early psychosis intervention for Australian indigenous communities: Indigenous

worker consultation and service model description. *Australasian Psychiatry* 21: 249–253.

Challis S, Nielssen O, Harris A, et al. (2013) Systematic meta-analysis of the risk factors for deliberate self-harm before and after treatment for first-episode psychosis. *Acta Psychiatrica Scandinavica* 127: 442–454.

Chalmers A, Harrison S, Mollison K, et al. (2012) Establishing sensory-based approaches in mental health inpatient care: A multidisciplinary approach. *Australasian Psychiatry* 20: 35–39.

Chanpattana W and Sackeim HA (2010) Electroconvulsive therapy in treatment-resistant schizophrenia: Prediction of response and the nature of symptomatic improvement. *The Journal of ECT* 26: 289–298.

Chanpattana W, Chakrabhand M, Buppanharun W, et al. (2000) Effects of stimulus intensity on the efficacy of bilateral ECT in schizophrenia: A preliminary study. *Biological Psychiatry* 48: 222–228.

Chanpattana W, Chakrabhand MS, Sackeim HA, et al. (1999) Continuation ECT in treatment-resistant schizophrenia: A controlled study. *The Journal of ECT* 15: 178–192.

Chen C, Huang M, Kao C, et al. (2013) Effects of adjunctive metformin on metabolic traits in nondiabetic clozapine-treated patients with schizophrenia and the effect of metformin discontinuation on body weight: A 24-week, randomized, double-blind, placebo-controlled study. *Journal of Clinical Psychiatry* 74: e424–e430.

Chilvers R, Macdonald G and Hayes A (2006) Supported housing for people with severe mental disorders. *The Cochrane Database of Systematic Reviews* 4: CD000453.

Chwastiak LA and Tek C (2009) The unchanging mortality gap for people with schizophrenia. *The Lancet* 374: 590–592.

Citrome L (2013) A review of the pharmacology, efficacy and tolerability of recently approved and upcoming oral antipsychotics: An evidence-based medicine approach. *CNS Drugs* 27: 879–911.

Clarke DM and Kissane DW (2002) Demoralization: Its phenomenology and importance. *Australian and New Zealand Journal of Psychiatry* 36: 733–742.

Clevenger CV and Plank TL (1997) Prolactin as an autocrine/paracrine factor in breast tissue. *Journal of Mammary Gland Biology and Neoplasia* 2: 59–68.

Cohen CI, Cohen GD, Blank K, et al. (2000) Schizophrenia and older adults. An overview: Directions for research and policy. *The American Journal of Geriatric Psychiatry* 8: 19–28.

Cohen LS, Viguera AC, McInerney KA, et al. (2015) Reproductive safety of second-generation antipsychotics: Current data from the Massachusetts General Hospital National Pregnancy Registry for atypical antipsychotics. *The American Journal of Psychiatry* 173: 263–270.

Coid J, Kirkbride J, Barker D, et al. (2008) Raised incidence rates of all psychoses among migrant groups: Findings from the East London first episode psychosis study. *Archives of General Psychiatry* 65: 1250–1258.

Combs DR, Adams SD, Penn DL, et al. (2007) Social Cognition and Interaction Training (SCIT) for inpatients with schizophrenia spectrum disorders: Preliminary findings. *Schizophrenia Research* 91: 112–116.

Cook JA, Copeland ME, Jonikas JA, et al. (2012) Results of a randomized controlled trial of mental illness self-management using Wellness Recovery Action Planning. *Schizophrenia Bulletin* 38: 881–891.

Cooper J, Mancuso SG, Borland R, et al. (2012) Tobacco smoking among people living with a psychotic illness: The second Australian survey of psychosis. *Australian and New Zealand Journal of Psychiatry* 46: 851–863.

Correll C, Sikich L, Reeves G, et al. (2013) Metformin for antipsychotic-related weight gain and metabolic abnormalities: When, for whom, and for how long? *The American Journal of Psychiatry* 170: 947–952.

Craig TK, Garety P, Power P, et al. (2004) The Lambeth Early Onset (LEO) Team: Randomised controlled trial of the effectiveness of specialised care for early psychosis. *British Medical Journal* 329: 1067.

Crawford MJ, Killaspy H, Barnes TR, et al. (2012) Group art therapy as an adjunctive treatment for people with schizophrenia: A randomised controlled trial (MATISSE). *Health Technology Assessment* 16(8): iii–iv, 1–76.

Crebbin K, Mitford E, Paxton R, et al. (2009) First-episode drug-induced psychosis: A medium term follow up study reveals a high-risk group. *Social Psychiatry and Psychiatric Epidemiology* 44: 710–715.

Cupina D, Patil S and Loo C (2013) Chronic catatonic schizophrenia treated successfully with right unilateral ultrabrief pulse electroconvulsive therapy: Case report. *The Journal of ECT* 29: 134–136.

Curtis J, Samaras K and Newall H (2012) *Positive Cardiometabolic Health: An Early Intervention Framework for Patients on Psychotropic Medication*. Sydney, NSW, Australia: New South Wales Government Health and Education and Training Institute.

Curtis J, Watkins A, Rosenbaum S, et al. (2015) Evaluating an individualized lifestyle and life skills intervention to prevent antipsychotic-induced weight gain in first-episode psychosis. *Early Intervention in Psychiatry*. Epub ahead of print 26 February. DOI: 10.1111/eip.12230.

Daumit GL, Dickerson FB, Wang N-Y, et al. (2013) A behavioral weight-loss intervention in persons with serious mental illness. *The New England Journal of Medicine* 368: 1594–1602.

Davis S, Papalia M-A, Norman RJ, et al. (2008) Safety and efficacy of a testosterone metered-dose transdermal spray for treating decreased sexual satisfaction in premenopausal women: A randomized trial. *Annals of Internal Medicine* 148: 569–577.

Dawe S, Seinen A and Kavanagh D (2000) An examination of the utility of the AUDIT in people with schizophrenia. *Journal of Studies on Alcohol* 61: 744–750.

De Hert M, Vancampfort D, Correll C, et al. (2011) Guidelines for screening and monitoring of cardiometabolic risk in schizophrenia: Systematic evaluation. *The British Journal of Psychiatry* 199: 99–105.

De Villiers T, Gass M, Haines C, et al. (2013) Global consensus statement on menopausal hormone therapy. *Climacteric* 16: 203–204.

Demjaha A, MacCabe JH and Murray RM (2012) How genes and environmental factors determine the different neurodevelopmental trajectories of schizophrenia and bipolar disorder. *Schizophrenia Bulletin* 38: 209–214.

Desmarais JE, Beauclair L and Margolese HC (2012) Anticholinergics in the era of atypical antipsychotics: Short-term or long-term treatment? *Journal of Psychopharmacology* 26: 1167–1174.

Dickerson FB and Lehman AF (2011) Evidence-based psychotherapy for schizophrenia: 2011 update. *The Journal of Nervous and Mental Disease* 199: 520–526.

Dieterich M, Irving CB, Park B, et al. (2010) Intensive case management for severe mental illness. *The Cochrane Database of Systematic Reviews* 10: CD007906.

Dodd S and Berk M (2006) The safety of medications for the treatment of bipolar disorder during pregnancy and the puerperium. *Current Drug Safety* 1: 25–33.

Dolan M, Castle D and McGregor K (2012) Criminally violent victimisation in schizophrenia spectrum disorders: The relationship to symptoms and substance abuse. *BMC Public Health* 12: 445.

Dold M, Li C, Gillies D, et al. (2013) Benzodiazepine augmentation of antipsychotic drugs in schizophrenia: A meta-analysis and Cochrane review of randomized controlled trials. *European Neuropsychopharmacology* 23: 1023–1033.

Drager LF, Togeiro SM, Polotsky VY, et al. (2013) Obstructive sleep apnea: A cardiometabolic risk in obesity and the metabolic syndrome. *Journal of the American College of Cardiology* 62: 569–576.

Drake R, Bond G and Becker D (2012) *Individual Placement and Support: An Evidence-Based Approach to Supported Employment*. New York: Oxford University Press.

Drake RE, Becker DR and Bond GR (2003) Recent research on vocational rehabilitation for persons with severe mental illness. *Current Opinion in Psychiatry* 16: 451–455.

Drake RE, Becker DR, Clark RE, et al. (1999) Research on the individual placement and support model of supported employment. *Psychiatric Quarterly* 70: 289–301.

Druss BG, Bradford WD, Rosenheck RA, et al. (2001) Quality of medical care and excess mortality in older patients with mental disorders. *Archives of General Psychiatry* 58: 565–572.

Dudgeon P, Milroy H and Walker R (2014) *Working Together: Aboriginal and Torres Strait Islander Mental Health and Wellbeing Principles and Practice*. Canberra, ACT, Australia: Commonwealth of Australia.

Dunne RA and McLoughlin DM (2012) Systematic review and meta-analysis of bifrontal electroconvulsive therapy versus bilateral and unilateral electroconvulsive therapy in depression. *World Journal of Biological Psychiatry* 13: 248–258.

Durie M (1998) *Whaiora: Māori Health Development*, 2nd Edition. Auckland, New Zealand: Oxford University Press.

Durie MH (1985) A Māori perspective of health. *Social Science & Medicine* 20: 483–486.

Dursun SM, Wildgust HJ, Strickland P, et al. (2008) The emerging physical health challenges of antipsychotic associated hyperprolactinaemia in patients with serious mental illness. *Journal of Psychopharmacology* 22(2 Suppl.): 3–5.

Eack SM, Mesholam-Gately RI, Greenwald DP, et al. (2013) Negative symptom improvement during cognitive rehabilitation: Results from a 2-year trial of Cognitive Enhancement Therapy. *Psychiatry Research* 209: 21–26.

Emsley R, Chiliza B and Asmal L (2013a) The evidence for illness progression after relapse in schizophrenia. *Schizophrenia Research* 148: 117–121.

Emsley R, Chiliza B, Asmal L, et al. (2013b) The nature of relapse in schizophrenia. *BMC Psychiatry* 13: 50.

Emsley R, Oosthuizen PP, Koen L, et al. (2012) Symptom recurrence following intermittent treatment in first-episode schizophrenia successfully treated for 2 years: A 3-year open-label clinical study. *Journal of Clinical Psychiatry* 73: e541–e547.

Eranti SV, MacCabe JH, Bundy H, et al. (2013) Gender difference in age at onset of schizophrenia: A meta-analysis. *Psychological Medicine* 43: 155–167.

Essali A, Al-Haj Haasan N and Li CRJ (2009) Clozapine versus typical neuroleptic medication for schizophrenia. *The Cochrane Database of Systematic Reviews* 1: CD000059.

Fazel S and Yu R (2011) Psychotic disorders and repeat offending: Systematic review and meta-analysis. *Schizophrenia Bulletin* 37: 800–810.

Fazel S, Zetterqvist J, Larsson H, et al. (2014) Antipsychotics, mood stabilisers, and risk of violent crime. *The Lancet* 384: 1206–1214.

Foley DL, Mackinnon A, Watts GF, et al. (2013) Cardiometabolic risk indicators that distinguish adults with psychosis from the general population, by age and gender. *PLoS ONE* 8: e82606.

Freitas C, Fregni F and Pascual-Leone A (2009) Meta-analysis of the effects of repetitive transcranial magnetic stimulation (rTMS) on negative and positive symptoms in schizophrenia. *Schizophrenia Research* 108: 11–24.

Freudenreich O, Schulz SC and Goff DC (2009) Initial medical work-up of first-episode psychosis: A conceptual review. *Early Intervention in Psychiatry* 3: 10–18.

Frogley C, Taylor D, Dickens G, et al. (2012) A systematic review of the evidence of clozapine's anti-aggressive effects. *The International Journal of Neuropsychopharmacology* 15: 1351–1371.

Frueh B, Grubaugh A, Cusack KJ, et al. (2009) Exposure-based cognitive-behavioral treatment of PTSD in adults with schizophrenia or schizoaffective disorder: A pilot study. *Journal of Anxiety Disorders* 23: 665–675.

Fusar-Poli P, Bonoldi I, Yung AR, et al. (2012) Predicting psychosis: Meta-analysis of transition outcomes in individuals at high clinical risk. *Archives of General Psychiatry* 69: 220.

Fusar-Poli P, Borgwardt S, Bechdolf A, et al. (2013) The psychosis high-risk state: A comprehensive state-of-the-art review. *JAMA Psychiatry* 70: 107–120.

Gaines P, Bower A, Buckingham W, et al. (2003) *New Zealand Mental Health Classification and Outcomes Study: Final Report*. Auckland, New Zealand: Health Research Council of New Zealand.

Gairns S, Alvarez-Jimenez M, Hulbert C, et al. (2015) Perceptions of clinicians treating young people with first-episode psychosis for post-traumatic stress disorder. *Early Intervention in Psychiatry* 9: 12–20.

Gallego JA, Nielsen J, De Hert M, et al. (2012) Safety and tolerability of antipsychotic polypharmacy. *Expert Opinion on Drug Safety* 11: 527–542.

Galletly C and Crichton J (2011) Accomplishments of the thought disordered person: A case study in psychiatrist-patient interaction. *Medical Hypotheses* 77: 900–904.

Galletly CA, Foley DL, Waterreus A, et al. (2012) Cardiometabolic risk factors in people with psychotic disorders: The second Australian national survey of psychosis. *Australian and New Zealand Journal of Psychiatry* 46: 753–761.

Gami AS, Olson EJ, Shen WK, et al. (2013) Obstructive sleep apnea and the risk of sudden cardiac death: A longitudinal study of 10,701 adults. *Journal of the American College of Cardiology* 62: 610–616.

Gates J, Killackey E, Phillips L, et al. (2015) Mental health starts with physical health: Current status and future directions of non-pharmacological interventions to improve physical health in first-episode psychosis. *The Lancet Psychiatry* 2: 726–742.

Gaudiano BA and Herbert JD (2006) Acute treatment of inpatients with psychotic symptoms using Acceptance and Commitment Therapy: Pilot results. *Behaviour Research and Therapy* 44: 415–437.

Goff DC, Cather C, Evins AE, et al. (2005) Medical morbidity and mortality in schizophrenia: Guidelines for psychiatrists. *Journal of Clinical Psychiatry* 66: 183–194.

Gómez-de-Regil L, Kwapil TR, Manel Blanqué J, et al. (2010) Predictors of outcome in the early course of first-episode psychosis. *The European Journal of Psychiatry* 24: 87–97.

Goswami U, Kumar U and Singh B (2003) Efficacy of electroconvulsive therapy in treatment resistant schizophrenia: A double-blind study. *Indian Journal of Psychiatry* 45: 26–29.

Gottesman II and Bertelsen A (1989) Confirming unexpressed genotypes for schizophrenia: Risks in the offspring of Fischer's Danish identical and fraternal discordant twins. *Archives of General Psychiatry* 46: 867–872.

Granholm E, McQuaid JR, McClure FS, et al. (2005) A randomized, controlled trial of cognitive behavioral social skills training for middle-aged and older outpatients with chronic schizophrenia. *The American Journal of Psychiatry* 162: 520–529.

Green S, Girling DM, Lough S, et al. (1997) Service provision for elderly people with long-term functional illness. *Psychiatric Bulletin* 21: 353–357.

Grocke D, Bloch S and Castle D (2009) The effect of group music therapy on quality of life for participants living with a severe and enduring mental illness. *Journal of Music Therapy* 46: 90–104.

Grocke D, Bloch S, Castle D, et al. (2014) Group music therapy for severe mental illness: A randomized embedded-experimental mixed methods study. *Acta Psychiatrica Scandinavica* 130: 144–153.

Grossman LS, Harrow M, Rosen C, et al. (2006) Sex differences in outcome and recovery for schizophrenia and other psychotic and nonpsychotic disorders. *Psychiatric Services* 57: 844–850.

Grover S, Chakrabarti S, Ghormode D, et al. (2015) Catatonia in inpatients with psychiatric disorders: A comparison of schizophrenia and mood disorders. *Psychiatry Research* 229: 919–925.

Gruenberg E (1974) The epidemiology of schizophrenia. In: Arieti S (ed.) *American Handbook of Psychiatry*, 2nd Edition. New York: Basic Books. pp. 448–463.

Gupta P, Mullin K, Nielssen O, et al. (2013) Do former substance users with psychosis differ in their symptoms or function from non-substance users? A systematic meta-analysis. *Australian and New Zealand Journal of Psychiatry* 47: 524–537.

Gupta R, Assalman I and Bottlender R (2012) Menopause and schizophrenia. *Menopause International* 18: 10–14.

Gururajan A, Manning EE, Klug M, et al. (2012) Drugs of abuse and increased risk of psychosis development. *Australian and New Zealand Journal of Psychiatry* 46: 1120–1135.

Guy W (1976) *ECDEU Assessment Manual for Psychopharmacology – Revised (DHEW Publ No ADM 76–338)*. Rockville, MD: US Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs.

Haack S, Seeringer A, Thürmann PA, et al. (2009) Sex-specific differences in side effects of psychotropic drugs: Genes or gender? *Pharmacogenomics* 10: 1511–1526.

Haddad P and Wieck A (2004) Antipsychotic-induced hyperprolactinaemia: Mechanisms, clinical features and management. *Drugs* 64: 2291–2314.

Häfner H, Hambrecht M, Löffler W, et al. (1998) Is schizophrenia a disorder of all ages? A comparison of first episodes and early course across the life-cycle. *Psychological Medicine* 28: 351–365.

Halperin S, Nathan P, Drummond P, et al. (2000) A cognitive-behavioural, group-based intervention for social anxiety in schizophrenia. *Australasian Psychiatry* 34: 809–813.

Harris R, Tobias M, Jeffreys M, et al. (2006) Effects of self-reported racial discrimination and deprivation on Maori health and inequalities in New Zealand: Cross-sectional study. *The Lancet* 367: 2005–2009.

Harrison G, Hopper K, Craig T, et al. (2001) Recovery from psychotic illness: A 15- and 25-year international follow-up study. *The British Journal of Psychiatry* 178: 506–517.

Hasan A, Falkai P, Wobrock T, et al. (2015) World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia. Part 3: Update 2015 management of special circumstances: Depression, suicidality, substance use disorders and pregnancy and lactation. *World Journal of Biological Psychiatry* 16: 142–170.

Hasan A, Falkai P, Wobrock T, et al. (2012) World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia. Part 1: Update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. *World Journal of Biological Psychiatry* 13: 318–378.

Hasan A, Falkai P, Wobrock T, et al. (2013) World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia. Part 2: Update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects. *World Journal of Biological Psychiatry* 14: 2–44.

Hastrup LH, Kronborg C, Bertelsen M, et al. (2013) Cost-effectiveness of early intervention in first-episode psychosis: Economic evaluation of a randomised controlled trial (the OPUS study). *The British Journal of Psychiatry* 202: 35–41.

Haswell-Elkins M, Sebasio T, Hunter E, et al. (2007) Challenges of measuring the mental health of Indigenous Australians: Honouring ethical expectations and driving greater accuracy. *Australasian Psychiatry* 15: S29–S33.

Havaki-Kontaxaki BJ, Ferentinos PP, Kontaxakis VP, et al. (2006) Concurrent administration of clozapine and electroconvulsive therapy in clozapine-resistant schizophrenia. *Clinical Neuropharmacology* 29: 52–56.

guide.medlive.cn

Heffernan EB, Andersen KC, Dev A, et al. (2012) Prevalence of mental illness among Aboriginal and Torres Strait Islander people in Queensland prisons. *Medical Journal of Australia* 197: 37–41.

Hegarty JD, Baldessarini RJ, Tohen M, et al. (1994) One hundred years of schizophrenia: A meta-analysis of the outcome literature. *The American Journal of Psychiatry* 151: 1409–1416.

Henderson AR and Kemp V (2013) Australian consumer perceptions of peer support. *Asia-Pacific Psychiatry* 5: 152–156.

Hennen J and Baldessarini RJ (2005) Suicidal risk during treatment with clozapine: A meta-analysis. *Schizophrenia Research* 73: 139–145.

Ho BC and Andreasen NC (2001) Long delays in seeking treatment for schizophrenia. *The Lancet* 357: 898–900.

Hogarty GE, Greenwald D, Ulrich RF, et al. (1997) Three-year trials of personal therapy among schizophrenic patients living with or independent of family, II: Effects on adjustment of patients. *The American Journal of Psychiatry* 154: 1514–1524.

Holland C, Dudgeon P, Milroy H, et al. (2013) The mental health and social and emotional wellbeing of Aboriginal and Torres Strait Islander peoples, families and communities. Available at: http://www.mentalhealthcommission.gov.au/our-reports/our-national-report-cards/2012-report-card/supporting-documents.aspx (accessed 16 March 2016).

Hopper K, Harrison G, Janca A, et al. (2007) *Recovery from Schizophrenia: An International Perspective: A Report from the WHO Collaborative Project, the International Study of Schizophrenia*. Oxford: Oxford University Press.

Hor K and Taylor M (2010) Suicide and schizophrenia: A systematic review of rates and risk factors. *Journal of Psychopharmacology* 24: 81–90.

Howard R, Rabins PV, Seeman MV, et al. (2000) Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: An international consensus. The International Late-Onset Schizophrenia Group. *The American Journal of Psychiatry* 157: 172–178.

Hunt GE, Siegfried N, Morley K, et al. (2013) Psychosocial interventions for people with both severe mental illness and substance misuse. *The Cochrane Database of Systematic Reviews* 10: CD001088.

Hunter E (2007) Disadvantage and discontent: A review of issues relevant to the mental health of rural and remote Indigenous Australians. *Australian Journal of Rural Health* 15: 88–93.

Hunter E (2013) Indicators of psychoses or psychoses as indicators: The relationship between Indigenous social disadvantage and serious mental illness. *Australasian Psychiatry* 21: 22–26.

Hunter E (2014) Mental health in Indigenous settings: Challenges for clinicians. *Australian Family Physician* 43: 26–28.

Hunter EM, Gynther BD, Anderson CJ, et al. (2012) Psychosis in Indigenous populations of Cape York and the Torres Strait. *Medical Journal of Australia* 196: 133–135.

Hurford IM, Marder SR, Keefe RS, et al. (2011) A brief cognitive assessment tool for schizophrenia: Construction of a tool for clinicians. *Schizophrenia Bulletin* 37: 538–545.

Inder WJ and Castle D (2011) Antipsychotic-induced hyperprolactinaemia. *Australian and New Zealand Journal of Psychiatry* 45: 830–837.

International First Episode Vocational Recovery Group (2008) *Meaningful Lives: Supporting Young People with Psychosis in Education, Training and Employment*. Leeds: International First Episode Vocational Recovery Group and National Institute for Mental Health in England.

International Physical Health in Youth (iphYs) Working Group (2013) *Healthy Active Lives (HeAL) Consensus Statement 2013*. iphYs. Available at: http://www.iphys.org.au (accessed 16th March 2016).

Ioasa-Martin I and Moore LJ (2012) Problems with non-adherence to antipsychotic medication in Samoan new Zealanders: A literature review. *International Journal of Mental Health Nursing* 21: 386–392.

Irving CB, Mumby-Croft R and Joy L (2006) Polyunsaturated fatty acid supplementation for schizophrenia. *The Cochrane Database of Systematic Reviews* 3: CD001257.

Ising HK, Smit F, Veling W, et al. (2015) Cost-effectiveness of preventing first-episode psychosis in ultra-high-risk subjects: Multi-centre randomized controlled trial. *Psychological Medicine* 45: 1435–1446.

Iyer SN, Mangala R, Anitha J, et al. (2011) An examination of patient-identified goals for treatment in a first-episode programme in Chennai, India. *Early Intervention in Psychiatry* 5: 360–365.

Jaaskelainen E, Juola P, Hirvonen N, et al. (2013) A systematic review and meta-analysis of recovery in schizophrenia. *Schizophrenia Bulletin* 39: 1296–1306.

Jablensky A (2006) Subtyping schizophrenia: Implications for genetic research. *Molecular Psychiatry* 11: 815–836.

Jablensky A, McGrath J, Herrman H, et al. (2000) Psychotic disorders in urban areas: An overview of the Study on Low Prevalence Disorders. *Australian and New Zealand Journal of Psychiatry* 34: 221–236.

Jablensky A, Sartorius N, Ernberg G, et al. (1992) Schizophrenia: Manifestations, incidence and course in different cultures: A World Health Organization ten-country study. *Psychological Medicine* 20: 1–97.

Jarskog LF, Hamer RM, Catellier DJ, et al. (2013) Metformin for weight loss and metabolic control in overweight outpatients with schizophrenia and schizoaffective disorder. *The American Journal of Psychiatry* 170: 1032–1040.

Jauhar S, McKenna P, Radua J, et al. (2014) Cognitive-behavioural therapy for the symptoms of schizophrenia: Systematic review and meta-analysis with examination of potential bias. *The British Journal of Psychiatry* 204: 20–29.

Jeppesen P, Petersen L, Thorup A, et al. (2005) Integrated treatment of first-episode psychosis: Effect of treatment on family burden: OPUS trial. *The British Journal of Psychiatry* 48: s85–s90.

Jeste DV, Twamley EW, Eyler Zorrilla LT, et al. (2003) Aging and outcome in schizophrenia. *Acta Psychiatrica Scandinavica* 107: 336–343.

Joa I, Johannessen JO, Auestad B, et al. (2008) The key to reducing duration of untreated first psychosis: Information campaigns. *Schizophrenia Bulletin* 34: 466–472.

Johnson M (2006) National patient safety report. *The Journal of Adult Protection* 8: 36–38.

Jones C, Hacker D, Cormac I, et al. (2012) Cognitive behaviour therapy versus other psychosocial treatments for schizophrenia. *The Cochrane Database of Systematic Reviews* 4: CD008712.

Kahn RS, Fleischhacker WW, Boter H, et al. (2008) Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: An open randomised clinical trial. *The Lancet* 371: 1085–1097.

Kake TR, Arnold R and Ellis P (2008) Estimating the prevalence of schizophrenia among New Zealand Maori: A capture-recapture approach. *Australasian Psychiatry* 42: 941–949.

Kay SR, Fiszbein A and Opler LA (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* 13: 261–276.

Keefe RS, Poe M, Walker TM, et al. (2006a) The relationship of the Brief Assessment of Cognition in Schizophrenia (BACS) to functional capacity and real-world functional outcome. *Journal of Clinical and Experimental Neuropsychology* 28: 260–269.

Keefe RS, Poe M, Walker TM, et al. (2006b) The Schizophrenia Cognition Rating Scale: An interview-based assessment and its relationship to cognition, real-world functioning, and functional capacity. *The American Journal of Psychiatry* 163: 426–432.

Kelleher I, Corcoran P, Keeley H, et al. (2013) Psychotic symptoms and population risk for suicide attempt: A prospective cohort study. *JAMA Psychiatry* 70: 940–948.

Kendzerska T, Gershon AS, Hawker G, et al. (2014) Obstructive sleep apnea and incident diabetes: A historical cohort study. *American Journal of Respiratory and Critical Care Medicine* 190: 218–225.

Khoury B, Lecomte T, Gaudiano BA, et al. (2013) Mindfulness interventions for psychosis: A meta-analysis. *Schizophrenia Research* 150: 176–184.

Killackey E and Yung AR (2007) Effectiveness of early intervention in psychosis. *Current Opinion in Psychiatry* 20: 121–125.

Killackey E, Jackson HJ and McGorry PD (2008) Vocational intervention in first-episode psychosis: A randomised controlled trial of individual

guide.medlive.cn

placement and support versus treatment as usual. *The British Journal of Psychiatry* 193: 114–120.

Killackey EJ, Jackson HJ, Gleeson J, et al. (2006) Exciting career opportunity beckons! Early intervention and vocational rehabilitation in first-episode psychosis: Employing cautious optimism. *Australian and New Zealand Journal of Psychiatry* 40: 951–962.

Kingi T and Durie M (1999) *Hua Oranga: A Māori Measure of Mental Health Outcome*. Palmerston North, New Zealand: Te Pumanawa Hauora, School of Māori Studies, Massey University.

Kingsep P, Nathan P and Castle D (2003) Cognitive behavioural group treatment for social anxiety in schizophrenia. *Schizophrenia Research* 63: 121–130.

Kinon B, Stauffer V, Kollack-Walker S, et al. (2008) Olanzapine versus aripiprazole for the treatment of agitation in acutely ill patients with schizophrenia. *Journal of Clinical Psychopharmacology* 28: 601–607.

Kinoshita Y, Furukawa TA, Kinoshita K, et al. (2013) Supported employment for adults with severe mental illness. *The Cochrane Database of Systematic Reviews* 9: CD008297.

Kirkbride JB, Fearon P, Morgan C, et al. (2006) Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: Findings from the 3-center AeSOP study. *Archives of General Psychiatry* 63: 250–258.

Kishimoto T, Agarwal V, Kishi T, et al. (2013) Relapse prevention in schizophrenia: A systematic review and meta-analysis of second-generation antipsychotics versus first-generation antipsychotics. *Molecular Psychiatry* 18: 53–66.

Kleinman A and Seeman D (2000) Personal experience of illness. In: Albrecht G, Fitzpatrick R and Scrimshaw S (eds) *Handbook of Social Studies in Health and Medicine*. London: SAGE, pp. 230–243.

Knox and Stimmel (2004) Clinical review of a long-acting, injectable formulation of risperidone. *Clinical Therapeutics* 26: 1994–2002.

Koga M (2003) Clinical factors related to gains in body mass index (BMI) among patients under long-term antipsychotic treatment. *Seishin Shinkeigaku Zasshi: Psychiatria et neurologia Japonica* 105: 473–488.

Koskinen J, Lohonen J, Koponen H, et al. (2009) Prevalence of alcohol use disorders in schizophrenia – A systematic review and meta-analysis. *Acta Psychiatrica Scandinavica* 120: 85–96.

Kulkarni J (2006) Psychotic disorders in women. In: Romans S and Seeman MV (eds) *Women's Mental Health – A Life Cycle Approach*. Philadelphia, PA: Lippincott, Williams & Wilkins. pp. 191–204.

Kulkarni J, de Castella A, Fitzgerald PB, et al. (2008a) Estrogen in severe mental illness: A potential new treatment approach. *Archives of General Psychiatry* 65: 955–960.

Kulkarni J, Gavrilidis E, Wang W, et al. (2014a) Estradiol for treatment-resistant schizophrenia: A large-scale randomized-controlled trial in women of child-bearing age. *Molecular Psychiatry* 20: 695–702.

Kulkarni J, Gurvich C, Lee SJ, et al. (2010) Piloting the effective therapeutic dose of adjunctive selective estrogen receptor modulator treatment in postmenopausal women with schizophrenia. *Psychoneuroendocrinology* 35: 1142–1147.

Kulkarni J, McCauley-Elsom K, Marston N, et al. (2008b) Preliminary findings from the national register of antipsychotic medication in pregnancy. *Australasian Psychiatry* 42: 38–44.

Kulkarni J, Worsley R, Gilbert H, et al. (2014b) A prospective cohort study of antipsychotic medications in pregnancy: The first 147 pregnancies and 100 one year old babies. *PLoS ONE* 9: e94788.

Kurtz MM and Richardson CL (2011) Social cognitive training for schizophrenia: A meta-analytic investigation of controlled research. *Schizophrenia Bulletin* 38: 1092–1104.

Kurtz MM, Bronfeld M and Rose J (2012) Cognitive and social cognitive predictors of change in objective versus subjective quality-of-life in rehabilitation for schizophrenia. *Psychiatry Research* 200: 102–107.

Lal C, Strange C and Bachman D (2012) Neurocognitive impairment in obstructive sleep apnea. *Chest* 141: 1601–1610.

Lambert T, Pantelis C and TRS Consensus Statement 2010 Editorial Panel (2010) Targeting treatment-refractory schizophrenia: A multidimensional outcomes approach to the diagnosis and management of incomplete recovery. Consensus statement 2010. Available at: www.trsconsensus.com.au/ (accessed 16 March 2016).

Large M, Sharma S, Compton MT, et al. (2011a) Cannabis use and earlier onset of psychosis: A systematic meta-analysis. *Archives of General Psychiatry* 68: 555–561.

Large M, Smith G and Nielssen O (2009) The relationship between the rate of homicide by those with schizophrenia and the overall homicide rate: A systematic review and meta-analysis. *Schizophrenia Research* 112: 123–129.

Large MM, Ryan C, Singh S, et al. (2011b) The predictive value of risk categorization in schizophrenia. *Harvard Review of Psychiatry* 19: 25–33.

Laursen TM (2011) Life expectancy among persons with schizophrenia or bipolar affective disorder. *Schizophrenia Research* 131: 101–104.

Lawrence D, Jablensky A, Holman C, et al. (2000) Mortality in Western Australian psychiatric patients. *Social Psychiatry and Psychiatric Epidemiology* 35: 341–347.

Leamy M, Bird V, Le Boutillier C, et al. (2011) Conceptual framework for personal recovery in mental health: Systematic review and narrative synthesis. *The British Journal of Psychiatry* 199: 445–452.

Leucht S, Cipriani A, Spineli L, et al. (2013) Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: A multiple-treatments meta-analysis. *The Lancet* 382: 951–962.

Leucht S, Helfer B, Dold M, et al. (2014) Carbamazepine for schizophrenia. *The Cochrane Database of Systematic Reviews* 5: CD001258.

Leucht S, Kissling W and McGrath J (2007) Lithium for schizophrenia. *The Cochrane Database of Systematic Reviews* 3: CD003834.

Lewine R (2004) At issue: Sex and gender in schizophrenia. *Schizophrenia Bulletin* 30: 755–762.

Light E, Kerridge I, Ryan C, et al. (2012) Community treatment orders in Australia: Rates and patterns of use. *Australasian Psychiatry* 20: 478–482.

Lin A, Nelson B and Yung A (2012) 'At-risk' for psychosis research: Where are we heading? *Epidemiology and Psychiatric Sciences* 1: 1–6.

Lohr JB, Eidt CA, Abdulrazzaq Alfaraj A, et al. (2015) The clinical challenges of akathisia. *CNS Spectrum* 20(Suppl. 1): 1–16.

Lommen M and Restifo K (2009) Trauma and posttraumatic stress disorder (PTSD) in patients with schizophrenia or schizoaffective disorder. *Community Mental Health Journal* 45: 485–496.

López-Moríñigo JD, Ramos-Ríos R, David AS, Dutta R (2012). Insight in schizophrenia and risk of suicide: a systematic update. *Comprehensive Psychiatry* 53: 313–322.

Lubman D, King J and Castle D (2010) Treating comorbid substance use disorders in schizophrenia. *International Review of Psychiatry* 22: 191–201.

Lyman DR, Kurtz MM, Farkas M, et al. (2014) Skill building: Assessing the evidence. *Psychiatric Services* 65: 727–738.

McAlpine DD (2003) Patterns of care for persons 65 years and older with schizophrenia. In: Cohen CI (ed.) *Schizophrenia into Later Life: Treatment, Research, and Policy*. Arlington, VA: American Psychiatric Publishing, pp. 3–17.

McCleery J, Jacoby R, Oppenheimer C, et al. (2008) Severe and enduring mental illness in old age. In: Denning T and Thomas A (eds) *The Oxford Textbook of Old Age Psychiatry*. Oxford: Oxford University Press, pp. 627–639.

McCrone P, Knapp M and Dhanasiri S (2009) Economic impact of services for first-episode psychosis: A decision model approach. *Early Intervention in Psychiatry* 3: 266–273.

McFarlane WR (2002) *Multifamily Groups in the Treatment of Severe Psychiatric Disorders*. New York: Guilford Press.

McGorry P, Killackey E, Lambert T, et al. (2005) Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of schizophrenia and related disorders. *Australian and New Zealand Journal of Psychiatry* 39: 1–30.

McGorry PD, Hickie IB, Yung AR, et al. (2006) Clinical staging of psychiatric disorders: A heuristic framework for choosing earlier, safer and more effective interventions. *Australian and New Zealand Journal of Psychiatry* 40: 616–622.

McGrath J, Saha S, Chant D, et al. (2008) Schizophrenia: A concise overview of incidence, prevalence, and mortality. *Epidemiologic Reviews* 30: 67–76.

McGrath J, Saha S, Welham J, et al. (2004) A systematic review of the incidence of schizophrenia: The distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Medicine* 2: 13.

McGrath P and Holewa H (2004) Mental health and palliative care: Exploring the ideological interface. *International Journal of Psychosocial Rehabilitation* 9: 107–119.

McGurk SR and Wykes T (2008) Cognitive remediation and vocational rehabilitation. *Psychiatric Rehabilitation Journal* 31: 350–359.

McKetin R, Lubman DI, Baker AL, et al. (2013) Dose-related psychotic symptoms in chronic methamphetamine users: Evidence from a prospective longitudinal study. *JAMA Psychiatry* 70: 319–324.

McNab C and Linszen D (2009) Family intervention in early psychosis. In: Jackson HJ and McGorry P (eds) *The Recognition and Management of Early Psychosis: A Preventative Approach*, 2nd Edition. Cambridge: Cambridge University Press. pp. 305–330.

Maglione JE, Thomas SE and Jeste DV (2014) Late-onset schizophrenia: Do recent studies support categorizing LOS as a subtype of schizophrenia? *Current Opinion in Psychiatry* 27: 173–178.

Malhi GS, Bassett D, Boyce P, et al. (2015) Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Australian and New Zealand Journal of Psychiatry* 49: 1087–1206.

Malla AK and Norman RMG (2002) Early intervention in schizophrenia and related disorders: Advantages and pitfalls. *Current Opinion in Psychiatry* 15: 17–23.

Maniglio R (2009) Severe mental illness and criminal victimization: A systematic review. *Acta Psychiatrica Scandinavica* 119: 180–191.

Marsh PJ, Langdon R, Harris A, et al. (2013) The case for social-cognitive remediation in schizophrenia: A life well lived is more than remission from psychosis. *Australian and New Zealand Journal of Psychiatry* 47: 512–515.

Marshall M and Lockwood A (2011) Assertive community treatment for people with severe mental disorders. *The Cochrane Database of Systematic Reviews* 4: CD001089.

Marsman A, van den Heuvel MP, Klomp DW, et al. (2013) Glutamate in schizophrenia: A focused review and meta-analysis of 1H-MRS studies. *Schizophrenia Bulletin* 39: 120–129.

Mathers CD and Loncar D (2006) Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Medicine* 3: e442.

Maust DT, Kim HM, Seyfried LS, et al. (2015) Antipsychotics, other psychotropics, and the risk of death in patients with dementia: Number needed to harm. *JAMA Psychiatry* 72: 438–445.

Medalia A and Revheim N (2002) *Dealing with Cognitive Dysfunction Associated with Psychiatric Disabilities: A Handbook for Families and Friends of Individuals with Psychiatric Disorders*. New York: New York State Office of Mental Health.

Meltzer HY, Alphs L, Green AI, et al. (2003) Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Archives of General Psychiatry* 60: 82–91.

Mendelsohn C, Kirby D and Castle D (2015) Smoking and mental illness: And update for psychiatrists. *Australasian Psychiatry* 23: 37–43.

Mental Health Commission (2001) *Recovery Competencies for New Zealand Mental Health Workers*. Wellington, New Zealand: Mental Health Commission.

Mental Health Council of Australia (MHCA) (2006) *Smart Services: Innovative Models of Mental Health Care in Australia and Overseas*. MHCA. Deakin: Australia.

Mental Health in Multicultural Australia (2013) Framework for Mental Health in Multicultural Australia. Available at: http://framework.mhima.org.au (accessed 16 March 2016).

Ministry of Māori Development (1993) *Te ara ahu whakamua: Strategic Direction for Māori Health: A Discussion Document*. Wellington, New Zealand: New Zealand Ministry of Maori Development.

Mitchell AJ, Vancampfort D, Sweers K, et al. (2013) Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders – A systematic review and meta-analysis. *Schizophrenia Bulletin* 39: 306–318.

Montgomery SA and Asberg M (1979) A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry* 134: 382–389.

Moore E, Mancuso SG, Slade T, et al. (2012) The impact of alcohol and illicit drugs on people with psychosis: The second Australian National Survey of Psychosis. *Australian and New Zealand Journal of Psychiatry* 46: 864–878.

Morgan V, McGrath J, Jablensky A, et al. (2014) Psychosis prevalence and physical, metabolic and cognitive co-morbidity: Data from the second Australian national survey of psychosis. *Psychological Medicine* 44: 2163–2176.

Morgan VA, Castle DJ and Jablensky AV (2008) Do women express and experience psychosis differently from men? Epidemiological evidence from the Australian National Study of Low Prevalence (Psychotic) Disorders. *Australian and New Zealand Journal of Psychiatry* 42: 74–82.

Morgan VA, Morgan F, Galletly C, et al. (2015) Sociodemographic, clinical and childhood correlates of adult violent victimisation in a large, national survey sample of people with psychotic disorders. *Social Psychiatry and Psychiatric Epidemiology* 51: 269–279.

Morgan VA, Waterreus A, Jablensky A, et al. (2011) *People Living with Psychotic Illness 2010. Report on the Second Australian National Survey*. Canberra, ACT, Australia: Australian Government Department of Health and Ageing.

Morgan VA, Waterreus A, Jablensky A, et al. (2012) People living with psychotic illness in 2010: The second Australian national survey of psychosis. *Australian and New Zealand Journal of Psychiatry* 46: 735–752.

Moritz S, Andreou C, Schneider BC, et al. (2014) Sowing the seeds of doubt: A narrative review on metacognitive training in schizophrenia. *Clinical Psychology Review* 34: 358–366.

Moritz S, Vitzthum F, Randjbar S, et al. (2010) Detecting and defusing cognitive traps: Metacognitive intervention in schizophrenia. *Current Opinion in Psychiatry* 23: 561–569.

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

Mössler K, Chen X, Heldal TO, et al. (2011) Music therapy for people with schizophrenia and schizophrenia-like disorders. *The Cochrane Database of Systematic Reviews* 12: CD004025.

Mueser K, Rosenberg S, Xie H, et al. (2008) A randomized controlled trial of cognitive-behavioral treatment for posttraumatic stress disorder in severe mental illness. *Journal of Consulting and Clinical Psychology* 76: 259–271.

Mueser KT and Gingerich S (2011) Relapse prevention and recovery in patients with psychosis: The role of psychiatric rehabilitation. *Psychiatric Times* 28: 66–71.

Mueser KT and Gingerich S (2013) Treatment of co-occurring psychotic and substance use disorders. *Social Work in Public Health* 28: 424–439.

Mueser KT, Deavers F, Penn DL, et al. (2013) Psychosocial treatments for schizophrenia. *Annual Review of Clinical Psychology* 9: 465–497.

Murch S, Tran N, Liew D, et al. (2013) Echocardiographic monitoring for clozapine cardiac toxicity: Lessons from real-world experience. *Australasian Psychiatry* 21: 258–261.

guide.medlive.cn

Myles H, Myles N, Antic NA, et al. (2016) Obstructive sleep apnea and schizophrenia: A systematic review to inform clinical practice. *Schizophrenia Research* 170: 222–225.

National Aboriginal and Torres Strait Islander Health Council (2004) *National Strategic Framework for Aboriginal and Torres Strait Islander Health, 2003–2013: Framework for Action by Governments*. Canberra, ACT, Australia: National Aboriginal and Torres Strait Islander Health Council.

National Health and Medical Research Council (NHMRC) (2009a) *Australian Guidelines to Reduce Health Risks from Drinking Alcohol*. Canberra, ACT, Australia: NHMRC.

National Health and Medical Research Council (NHMRC) (2009b) *NHMRC Additional Levels of Evidence and Grades for Recommendations for Developers of Guidelines*. Melbourne, VIC, Australia: NHMRC.

National Institute for Health and Care Excellence (NICE) (2014) *Psychosis and schizophrenia in adults: Treatment and management*. NICE clinical guideline 178. NICE, London, March.

National Mental Health Commission (2012) *A Contributing Life, the 2012 National Report Card on Mental Health and Suicide Prevention*. Sydney, NSW, Australia: National Mental Health Commission.

Neil AL, Carr VJ, Mihalopoulos C, et al. (2014) What difference a decade? The costs of psychosis in Australia in 2000 and 2010: Comparative results from the first and second Australian national surveys of psychosis. *Australian and New Zealand Journal of Psychiatry* 48: 237–248.

Neil AL, Carr VJ, Mihalopoulos C, et al. (2013) Costs of psychosis in 2010: Findings from the second Australian National Survey of Psychosis. *Australian and New Zealand Journal of Psychiatry* 48: 169–182.

Nestor P and Galletly C (2008) The employment of consumers in mental health services: Politically correct tokenism or genuinely useful? *Australasian Psychiatry* 16: 344–347.

New Zealand Ministry of Health (2008) *Te Puāwaiwhero: The Second Māori Mental Health and Addiction National Strategic Framework 2008–2015*. Wellington, New Zealand: New Zealand Government Ministry of Health.

New Zealand Ministry of Health (2012) *Rising to the Challenge: The Mental Health and Addiction Service Development Plan 2012–2017*. Wellington, New Zealand: New Zealand Government Ministry of Health.

Nguyen HT, Yamada AM and Dinh TQ (2012) Religious leaders' assessment and attribution of the causes of mental illness: An in-depth exploration of Vietnamese American Buddhist leaders. *Mental Health, Religion & Culture* 15: 511–527.

Nickelsen T, Lufkin EG, Lawrence Riggs B, et al. (1999) Raloxifene hydrochloride, a selective estrogen receptor modulator: Safety assessment of effects on cognitive function and mood in postmenopausal women. *Psychoneuroendocrinology* 24: 115–128.

Nielssen O and Large M (2010) Rates of homicide during the first episode of psychosis and after treatment: A systematic review and meta-analysis. *Schizophrenia Bulletin* 36: 702–712.

Nielssen O and Misrachi S (2005) Prevalence of psychoses on reception to male prisons in New South Wales. *Australian and New Zealand Journal of Psychiatry* 39: 453–459.

Nielssen O, Sara G, Lim Y, et al. (2013) Country of birth and hospital treatment for psychosis in New South Wales. *Social Psychiatry and Psychiatric Epidemiology* 48: 613–620.

Nielssen OB, Malhi GS, McGorry PD, et al. (2012) Overview of violence to self and others during the first episode of psychosis. *Journal of Clinical Psychiatry* 73: e580–e587.

Norman RM, Manchanda R, Malla AK, et al. (2011) Symptom and functional outcomes for a 5 year early intervention program for psychoses. *Schizophrenia Research* 129: 111–115.

Notman M and Nadelson C (2006) *Psychoanalytic Perspectives*. Toronto, ON, Canada: Lippincott, Williams & Wilkins.

Nuechterlein KH, Green M, Kern R, et al. (2008a) The MATRICS Consensus Cognitive Battery: Part 1: Test selection, reliability, and validity. *The American Journal of Psychiatry* 165: 203–213.

Nuechterlein KH, Subotnik KL, Turner LR, et al. (2008b) Individual placement and support for individuals with recent-onset schizophrenia: Integrating supported education and supported employment. *Psychiatric Rehabilitation Journal* 31: 340–349.

Nuechterlein KH, Subotnik KL, Ventura J, et al. (2012) The puzzle of schizophrenia: Tracking the core role of cognitive deficits. *Development and Psychopathology* 24: 529–536.

Olfson M, Gerhard T, Huang C, et al. (2015) Premature mortality among adults with schizophrenia in the United States. *JAMA Psychiatry* 72: 1172–1181.

Ormerod S, McDowell SE, Coleman JJ, et al. (2008) Ethnic differences in the risks of adverse reactions to drugs used in the treatment of psychoses and depression: A systematic review and meta-analysis. *Drug Safety* 31: 597–607.

Orygen Youth Health Research Centre (2011) *Early Psychosis Feasibility Study Report*. Canberra, ACT, Australia: National Advisory Council on Mental Health and Department of Health and Ageing.

Osborn DP, Limburg H, Walters K, et al. (2013) Relative incidence of common cancers in people with severe mental illness. Cohort study in the United Kingdom THIN primary care database. *Schizophrenia Research* 143: 44–49.

Overall J and Gorham D (1962) The Brief Psychiatric Rating Scale. *Psychological Reports* 10: 799–812.

Palmer B, Pankratz V and Bostwick J (2005) The lifetime risk of suicide in schizophrenia: A reexamination. *Archives of General Psychiatry* 62: 247–253.

Park AL, McCrone P and Knapp M (2014) Early intervention for first-episode psychosis: Broadening the scope of economic estimates. *Early Intervention in Psychiatry*. Epub ahead of print 17 April. DOI: 10.1111/eip.12149.

Patil SP, Schneider H, Schwartz AR, et al. (2007a) Adult obstructive sleep apnea: Pathophysiology and diagnosis. *Chest* 132: 325–337.

Patil ST, Zhang L, Martenyi F, et al. (2007b) Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: A randomized Phase 2 clinical trial. *Nature Medicine* 13: 1102–1107.

Paton C and Esop R (2005) Managing clozapine-induced neutropenia with lithium. *Psychiatric Bulletin* 29: 186–188.

Penttilä M, Jääskeläinen E, Hirvonen N, et al. (2014) Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: Systematic review and meta-analysis. *The British Journal of Psychiatry* 205: 88–94.

Petrides G, Malur C, Braga RJ, et al. (2015) Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: A prospective, randomized study. *The American Journal of Psychiatry* 172: 52–58.

Petty RG (1999) Prolactin and antipsychotic medications: Mechanism of action. *Schizophrenia Research* 35: S67–S73.

Peuskens J, Pani L, Detraux J, et al. (2014) The effects of novel and newly approved antipsychotics on serum prolactin levels: A comprehensive review. *CNS Drugs* 28: 421–453.

Pharoah F, Mari J, Rathbone J, et al. (2010) Family intervention for schizophrenia. *The Cochrane Database of Systematic Reviews* 12: CD000088.

Phutane VH, Thirthalli J, Muralidharan K, et al. (2013) Double-blind randomized controlled study showing symptomatic and cognitive superiority of bifrontal over bitemporal electrode placement during electroconvulsive therapy for schizophrenia. *Brain Stimulation* 6: 210–217.

Pilling S, Bebbington P, Kuipers E, et al. (2002) Psychological treatments in schizophrenia: I. Meta-analysis of family intervention and cognitive behaviour therapy. *Psychological Medicine* 32: 763–782.

Pitt V, Lowe D, Hill S, et al. (2013) Consumer-providers of care for adult clients of statutory mental health services. *The Cochrane Database of Systematic Reviews* 3: CD004807.

guide.medlive.cn

Pokos V and Castle DJ (2006) Prevalence of comorbid anxiety disorders in schizophrenia spectrum disorders: A literature review. *Current Psychiatry Reviews* 2: 285–307.

Porcelli S, Balzarro B and Serretti A (2012) Clozapine resistance: Augmentation strategies. *European Neuropsychopharmacology* 22: 165–182.

Power PJR, Bell RJ, Mills R, et al. (2003) Suicide prevention in first epi-sode psychosis: The development of a randomised controlled trial of cognitive therapy for acutely suicidal patients with early psychosis. *Australian and New Zealand Journal of Psychiatry* 37: 414–420.

Prikryl R, Kasparek T, Skotakova S, et al. (2007) Treatment of nega-tive symptoms of schizophrenia using repetitive transcranial mag-netic stimulation in a double-blind, randomized controlled study. *Schizophrenia Research* 95: 151–157.

Procter N (2007) Mental health emergencies. In: Curtis K, Ramsden C and Friendship J (eds) *Emergency and Trauma Nursing*. New York: Elsevier Press. pp. 625–642.

Procter N, Babakarkhi A, Baker A, et al. (2014) Mental health of people of migrant and refugee background. In: Procter N, Harmer H, McGarry D, et al. (eds) *Mental Health: A Person Centred Approach*. Melbourne, VIC, Australia: Cambridge University Press. pp. 197–214.

Psychotropic Writing Group (2013) *Therapeutic Guidelines – Psychotropic: Version 7*. Melbourne, VIC, Australia: Therapeutic Guidelines Limited.

Quinn J, Meagher D, Murphy P, et al. (2001) Vulnerability to invol-untary movements over a lifetime trajectory of schizophrenia approaches 100%, in association with executive (frontal) dysfunction. *Schizophrenia Research* 49: 79–87.

Raha S, Taylor VH and Holloway AC (2012) Effect of atypical antip-sychotics on fetal growth: Is the placenta involved? *Journal of Pregnancy* 2012: 315203.

Ramsay CE, Broussard B, Goulding SM, et al. (2011) Life and treatment goals of individuals hospitalized for first-episode nonaffective psy-chosis. *Psychiatry Research* 189: 344–348.

Randolph C, Tierney MC, Mohr E, et al. (1998) The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Preliminary clinical validity. *Journal of Clinical and Experimental Neuropsychology* 20: 310–319.

Raudino A, Carr VJ, Bush R, et al. (2014) Patterns of service utilisation in psychosis: Findings of the 2010 Australian national survey of psycho-sis. *Australian and New Zealand Journal of Psychiatry* 48: 341–351.

Read J, van Os J, Morrison AP, et al. (2005) Childhood trauma, psychosis and schizophrenia: A literature review with theoretical and clinical implications. *Acta Psychiatrica Scandinavica* 112: 330–350.

Rinaldi M, Killackey E, Smith J, et al. (2010) First episode psychosis and employment: A review. *International Review of Psychiatry* 22: 148–162.

Roberts DL, Combs DR, Willoughby M, et al. (2014) A randomized, controlled trial of Social Cognition and Interaction Training (SCIT) for outpatients with schizophrenia spectrum disorders. *The British Journal of Clinical Psychology* 53: 281–298.

Robinson D, Woerner MG, Alvir JMJ, et al. (1999) Predictors of relapse following response from a first episode of schizophrenia or schizoaf-fective disorder. *Archives of General Psychiatry* 56: 241–247.

Robson B and Harris R (2007) *Hauora: Māori Standards of Health IV: A Study of the Years 2000–2005*. Wellington, New Zealand: Te Rōpū Rangahau Hauora a Eru Pōmare.

Rodriguez-Ferrera S, Vassilas CA and Haque S (2004) Older people with schizophrenia: A community study in a rural catchment area. *International Journal of Geriatric Psychiatry* 19: 1181–1187.

Romme M and Escher S (2012) *Psychosis as a Personal Crisis: An Experience-Based Approach*. London: Routledge.

Ronaldson KJ, Fitzgerald PB, Taylor AJ, et al. (2011) A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. *Australian and New Zealand Journal of Psychiatry* 45: 458–465.

Sackeim HA, Prudic J, Fuller R, et al. (2006) The cognitive effects of electroconvulsive therapy in community settings. *Neuropsychopharmacology* 32: 244–254.

Saha S, Chant D and McGrath J (2007) A systematic review of mortality in schizophrenia: Is the differential mortality gap worsening over time? *Archives of General Psychiatry* 64: 1123–1131.

Saha S, Chant D, Welham J, et al. (2005) A systematic review of the preva-lence of schizophrenia. *PLoS Medicine* 2: e141.

Sanders D, Kydd R, Morunga E, et al. (2011) Differences in patients' perceptions of schizophrenia between Māori and New Zealand Europeans. *Australian and New Zealand Journal of Psychiatry* 45: 483–488.

Sands R (1995) The parenting experience of low-income single women with serious mental disorders. *Families in Society* 76: 86–96.

Sara GE, Burgess PM, Malhi GS, et al. (2014) Cannabis and stimulant disorders and readmission 2 years after first-episode psychosis. *The British Journal of Psychiatry* 204: 448–453.

Sara GE, Large MM, Matheson SL, et al. (2015) Stimulant use disorders in people with psychosis: A meta-analysis of rate and factors affect-ing variation. *Australian and New Zealand Journal of Psychiatry* 49: 106–117.

Sartorius N, Jablensky A, Korten A, et al. (1986) Early manifestations and first-contact incidence of schizophrenia in different cultures. A preliminary report on the initial evaluation phase of the WHO Collaborative Study on determinants of outcome of severe mental disorders. *Psychological Medicine* 16: 909–928.

Schimmelmann B, Conus P, Cotton S, et al. (2012) Prevalence and impact of cannabis use disorders in adolescents with early onset first episode psychosis. *European Psychiatry* 27: 463–469.

Schirmbeck F, Esslinger C, Rausch F, et al. (2011) Antiserotonergic antip-sychotics are associated with obsessive-compulsive symptoms in schizophrenia. *Psychological Medicine* 41: 2361–2373.

Schooler NR (2005) Relapse prevention and recovery in the treatment of schizophrenia. *Journal of Clinical Psychiatry* 67: 19–23.

Schwarz C, Volz A, Li C, et al. (2008) Valproate for schizophrenia. *The Cochrane Database of Systematic Reviews* 3: CD004028.

Seeman MV (2009) Secondary effects of antipsychotics: Women at greater risk than men. *Schizophrenia Bulletin* 35: 937–948.

Seeman MV (2012) Treating schizophrenia at the time of menopause. *Maturitas* 72: 117–120.

Seeman MV (2013a) Clinical interventions for women with schizophre-nia: Pregnancy. *Acta Psychiatrica Scandinavica* 127: 12–22.

Seeman MV (2013b) Women and schizophrenia: New findings. *Neuropsychiatry* 3: 423–431.

Seeman MV and Lang M (1990) The role of estrogens in schizophrenia gender differences. *Schizophrenia Bulletin* 16: 185–194.

Seeman MV and Seeman P (2014) Is schizophrenia a dopamine supersen-sitivity psychotic reaction? *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 48: 155–160.

Seikkula J (2002) Open dialogues with good and poor outcomes for psychotic crises: Examples from families with violence. *Journal of Marital and Family Therapy* 28: 263–274.

Selten J-P, van der Ven E, Rutten BP, et al. (2013) The social defeat hypothesis of schizophrenia: An update. *Schizophrenia Bulletin* 39: 1180–1186.

Shanks V, Williams J, Leamy M, et al. (2013) Measures of personal recov-ery: A systematic review. *Psychiatric Services* 64: 974–980.

Sharma V (2008) Treatment of postpartum psychosis: Challenges and opportunities. *Current Drug Safety* 3: 76–81.

Shawyer F, Farhall J, Mackinnon A, et al. (2012) A randomised controlled trial of acceptance-based cognitive behavioural therapy for com-mand hallucinations in psychotic disorders. *Behaviour Research and Therapy* 50: 110–121.

Sienaert P, Dhossche DM, Vancampfort D, et al. (2014) A clinical review of the treatment of catatonia. *Frontiers in Psychiatry* 5: 181.

guide.medlive.cn

Simeone JC, Ward AJ, Rotella P, et al. (2015) An evaluation of variation in published estimates of schizophrenia prevalence from 1990 horizontal line 2013: A systematic literature review. *BMC Psychiatry* 15: 193.

Sin J and Norman I (2013) Psychoeducational interventions for family members of people with schizophrenia: A mixed-method systematic review. *Journal of Clinical Psychiatry* 74: e1145–e1162.

Siris SG (2000) Depression in schizophrenia: Perspective in the era of 'atypical' antipsychotic agents. *The American Journal of Psychiatry* 157: 1379–1389.

Slade M (2009) The contribution of mental health services to recovery. *Journal of Mental Health* 18: 367–371.

Slade M (2013) *100 Ways to Support Recovery: A Guide for Mental Health Professionals*. London: Rethink Mental Illness.

Soares C (2008) Practical strategies for diagnosing and treating depression in women: Menopausal transition. *Journal of Clinical Psychiatry* 69: e30.

Social Health Reference Group for National Aboriginal and Torres Strait Islander Health Council and National Mental Health Working Group (2004) *Social and Emotional Well Being Framework: A National Strategic Framework for Aboriginal and Torres Strait Islander Peoples' Mental Health and Social and Emotional Well-Being 2004–2009*. Canberra, ACT, Australia: Australian Government Department of Health and Ageing.

Sommer IE, Begemann MJH, Temmerman A, et al. (2012) Pharmacological augmentation strategies for schizophrenia patients with insufficient response to clozapine: A quantitative literature review. *Schizophrenia Bulletin* 38: 1003–1011.

Stafford MR, Jackson H, Mayo-Wilson E, et al. (2013) Early interventions to prevent psychosis: Systematic review and meta-analysis. *British Medical Journal* 346: f185.

Stanley SH and Laugharne JD (2014) Physical health algorithms for mental health care. *Australian and New Zealand Journal of Psychiatry* 48: 889–894.

Stefanis N, Dragovic M, Power B, et al. (2014) The effect of drug use on the age at onset of psychotic disorders in an Australian cohort. *Schizophrenia Research* 156: 211–216.

Strauss J (2013) Reconceptualizing schizophrenia. *Schizophrenia Bulletin* 40(Suppl. 2): S97–100.

Su C-Y, Tsai P-C, Su W-L, et al. (2011) Cognitive profile difference between Allen Cognitive Levels 4 and 5 in schizophrenia. *The American Journal of Occupational Therapy* 65: 453–461.

Suaalii-Sauni T, Wheeler A, Saafi E, et al. (2009) Exploration of Pacific perspectives of Pacific models of mental health service delivery in New Zealand. *Pacific Health Dialog* 15: 18–27.

Sullivan PF, Daly MJ and O'Donovan M (2012) Genetic architectures of psychiatric disorders: The emerging picture and its implications. *Nature Reviews Genetics* 13: 537–551.

Tani H, Uchida H, Fujii Y, et al. (2013) Interventions to reduce antipsychotic polypharmacy: A systematic review. *Schizophrenia Research* 143: 215–220.

Tarur Padinjareveettil AM, Rogers J, Loo C, et al. (2014) Transcranial direct current stimulation to enhance cognitive remediation in schizophrenia. *Brain Stimulation* 8: 307–309.

Taylor D, Paton C and Kapur S (2015) *The Maudsley Prescribing Guidelines in Psychiatry*. Chichester: John Wiley & Sons.

Taylor P and Fleminger J (1980) ECT for schizophrenia. *The Lancet* 315: 1380–1383.

Te Pou o Te Whakaaro Nui (2009) *Real skills plus Seitapu. Working with Pacific Peoples*. Auckland, New Zealand: Le Va, Pasifi ka within Te Pou, The National Centre of Mental Health Research, Information and Workforce Development.

Te Rau Matatini and The Werry Centre (2004) Te Rau Tipu Māori. In: *Child and Adolescent Mental Health Workforce Development conference*, Palmerston North, New Zealand.

Teesson M, Hodder T and Buhrich N (2004) Psychiatric disorders in homeless men and women in inner Sydney. *Australian and New Zealand Journal of Psychiatry* 38: 162–168.

Ten Velden Hegelstad W, Larsen TK, Auestad B, et al. (2012) Long-term follow-up of the TIPS early detection in psychosis study: Effects on 10-year outcome. *The American Journal of Psychiatry* 169: 374–380.

Tenback D, Pijl B, Smeets H, et al. (2012) All-cause mortality and medication risk factors in schizophrenia: A prospective cohort study. *Journal of Clinical Psychopharmacology* 32: 31–35.

Tharyan P and Adams C (2005) Electroconvulsive therapy for schizophrenia. *The Cochrane Database of Systematic Reviews* 2: CD000076.

Thibaut F, Boutros N, Jarema M, et al. (2015) Consensus paper of the WFSBP Task Force on Biological Markers: Criteria for biomarkers and endophenotypes of schizophrenia. Part I: Neurophysiology. *World Journal of Biological Psychiatry* 16: 280–290.

Thomas N, Shawyer F, Castle D, et al. (2014) A randomised controlled trial of acceptance and commitment therapy (ACT) for psychosis: Study protocol. *BMC Psychiatry* 14: 198.

Thornicroft G (2011) Physical health disparities and mental illness: The scandal of premature mortality. *The British Journal of Psychiatry* 199: 441–442.

Thorup A, Petersen L, Jeppesen P, et al. (2005) Integrated treatment ameliorates negative symptoms in first episode psychosis – Results from the Danish OPUS trial. *Schizophrenia Research* 79: 95–105.

Tognin S, Riecher-Rössler A, Meisenzahl E, et al. (2014) Reduced parahippocampal cortical thickness in subjects at ultra-high risk for psychosis. *Psychological Medicine* 44: 489–498.

Tosh G, Clifton AV, Xia J, et al. (2014) Physical health care monitoring for people with serious mental illness. *The Cochrane Database of Systematic Reviews* 17: CD008298.

Tse L, Barr AM, Scarapicchia V, et al. (2015) Neuroleptic malignant syndrome: A review from a clinically oriented perspective. *Current Neuropharmacology* 13: 395–406.

Twamley EW, Doshi RR, Nayak GV, et al. (2002) Generalized cognitive impairments, ability to perform everyday tasks, and level of independence in community living situations of older patients with psychosis. *The American Journal of Psychiatry* 159: 2013–2020.

Usall J, Suarez D, Haro JM, et al. (2007) Gender differences in response to antipsychotic treatment in outpatients with schizophrenia. *Psychiatry Research* 153: 225–231.

Vahia IV, Palmer BW, Depp C, et al. (2010) Is late-onset schizophrenia a subtype of schizophrenia? *Acta Psychiatrica Scandinavica* 122: 414–426.

Van der Gaag M, Smit F, Bechdolf A, et al. (2013) Preventing a first episode of psychosis: Meta-analysis of randomized controlled prevention trials of 12 month and longer-term follow-ups. *Schizophrenia Research* 149: 56–62.

Van der Gaag M, Valmaggia LR and Smit F (2014) The effects of individually tailored formulation-based cognitive behavioural therapy in auditory hallucinations and delusions: A meta-analysis. *Schizophrenia Research* 156: 30–37.

Varese F, Smeets F, Drukker M, et al. (2012) Childhood adversities increase the risk of psychosis: A meta-analysis of patient-control, prospective- and cross-sectional cohort studies. *Schizophrenia Bulletin* 38: 661–671.

Vassos E, Pedersen CB, Murray RM, et al. (2012) Meta-analysis of the association of urbanicity with schizophrenia. *Schizophrenia Bulletin* 38: 1118–1123.

Velligan DI, Diamond PM, Mintz J, et al. (2008) The use of individually tailored environmental supports to improve medication adherence and outcomes in schizophrenia. *Schizophrenia Bulletin* 34: 483–493.

Velligan DI, DiCocco M, Bow-Thomas CC, et al. (2004) A brief cognitive assessment for use with schizophrenia patients in community clinics. *Schizophrenia Research* 71: 273–283.

Velligan DI, Mintz J, Sierra C, et al. (2015) The Daily Activity Report (DAR) a novel measure of functional outcome for serious mental illness. *Schizophrenia Bulletin*. DOI: 10.1093/schbul/sbv185.

Ventura J, Reise SP, Keefe RS, et al. (2010) The Cognitive Assessment Interview (CAI): Development and validation of an empirically

guide.medlive.cn

derived, brief interview-based measure of cognition. *Schizophrenia Research* 121: 24–31.

Waddington JL (1995) Psychopathological and cognitive correlates of tardive dyskinesia in schizophrenia and other disorders treated with neuroleptic drugs. *Advances in Neurology* 65: 211–229.

Waghorn G, Saha S, Harvey C, et al. (2012) 'Earning and learning' in those with psychotic disorders: The second Australian national survey of psychosis. *Australian and New Zealand Journal of Psychiatry* 46: 774–785.

Walker E and Bollini AM (2002) Pubertal neurodevelopment and the emergence of psychotic symptoms. *Schizophrenia Research* 54: 17–23.

Weickert TW, Weinberg D, Lenroot R, et al. (2015) Adjunctive raloxifene treatment improves attention and memory in men and women with schizophrenia. *Molecular Psychiatry* 20: 685–694.

Williams J, Leamy M, Bird V, et al. (2012) Measures of the recovery orientation of mental health services: Systematic review. *Social Psychiatry and Psychiatric Epidemiology* 47: 1827–1835.

Wisdom JP, Manuel JI and Drake RE (2011) Substance use disorder among people with first-episode psychosis: A systematic review of course and treatment. *Psychiatric Services* 62: 1007–1012.

World Health Organization (WHO) (1992) *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: WHO.

Wunderink L, Nieboer RM, Wiersma D, et al. (2013) Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: Long-term follow-up of a 2-year randomized clinical trial. *JAMA Psychiatry* 70: 913–920.

Wykes T, Huddy V, Cellard C, et al. (2011) A meta-analysis of cognitive remediation for schizophrenia: Methodology and effect sizes. *The American Journal of Psychiatry* 168: 472–485.

Wykes T, Steel C, Everitt B, et al. (2008) Cognitive behavior therapy for schizophrenia: Effect sizes, clinical models, and methodological rigor. *Schizophrenia Bulletin* 34: 523–537.

Xia J, Merinder LB and Belgamwar MR (2011) Psychoeducation for schizophrenia. *The Cochrane Database of Systematic Reviews* 6: CD002831.

Yassa R and Jeste DV (1992) Gender differences in tardive dyskinesia. *Schizophrenia Bulletin* 18: 701–715.

Yee NY, Large MM, Kemp RI, et al. (2011) Severe non-lethal violence during psychotic illness. *Australian and New Zealand Journal of Psychiatry* 45: 466–472.

Yonkers KA, Kando JC, Cole JO, et al. (1992) Gender differences in pharmacokinetics and pharmacodynamics of psychotropic medication. *The American Journal of Psychiatry* 149: 587–595.

Yuen K, Harrigan SM, Mackinnon AJ, et al. (2014) Long-term follow-up of all-cause and unnatural death in young people with first-episode psychosis. *Schizophrenia Research* 159: 70–75.

Yung AR. (2003) Commentary: The schizophrenia prodrome: A high-risk concept. *Schizophrenia Bulletin* 29: 859–865.

Zeller SL and Rhoades RW (2010) Systematic reviews of assessment measures and pharmacologic treatments for agitation. *Clinical Therapeutics* 32: 403–425.

Zhang J-P, Gallego JA, Robinson DG, et al. (2013a) Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: A systematic review and meta-analysis. *The International Journal of Neuropsychopharmacology* 16: 1205–1218.

Zhang Y, Liang W, Yang S, et al. (2013b) Repetitive transcranial magnetic stimulation for hallucination in schizophrenia spectrum disorders: A meta-analysis. *Neural Regeneration Research* 8: 2666–2676.

Appendix 1

Name	Declaration of interests
Professor Cherrie Galletly	Grants: National Health and Medical Research Council of Australia Clinical trials: Bristol-Myers Squibb Research & Development, Janssen Research & Development, ICON Clinical Research P/L, Envivo Pharmaceuticals/INC Research Professional fees: Lundbeck, Janssen-Cilag
Professor David Castle	Grants: National Health and Medical Research Council of Australia Grants and personal fees: Eli Lilly, Janssen-Cilag, Roche, Allergen, Bristol-Myers Squibb, Pfizer, Lundbeck, AstraZeneca, Hospira Personal Fees: Organon, Sanofi-Aventis, Wyeth, Servier. Advisory Board Member: Lu AA21004: Lundbeck, Varenicline: Pfizer, Asenapine, Seroquel: AstraZeneca, Bitopertin: Roche, Lisdexamefetamine: Shire, Paliperidone LAI: Janssen, Lurasidone: Servier
Dr Frances Dark	No conflict of interest
Dr Verity Humberstone	No conflict of interest
Professor Assen Jablensky	No conflict of interest
Professor Eoin Killackey	No conflict of interest
Professor Jayashri Kulkarni	No conflict of interest
Professor Patrick McGorry	Grants: National Health and Medical Research Council of Australia, Colonial Foundation, Novartis Grants and personal fees: AstraZeneca, Eli Lilly, Janssen-Cilag, Pfizer Personal fees: Bristol-Myers Squibb
Dr Olav Nielssen	Professional fees: Lundbeck
Ms Nga Tran	No conflict of interest

guide.medlive.cn