

# Schizophrenia and depression

Schizophrenia is a disorder characterised by positive symptoms (delusions and hallucinations), negative symptoms (apathy, withdrawal, paucity of thought and restriction of affect), disorganisation symptoms (disorganised thoughts and actions)<sup>1</sup> and cognitive impairment (memory, attention, working memory, problem solving, processing speed and social cognition).<sup>2</sup> Many people with schizophrenia have a limited and isolated existence, in addition to high rates of unemployment, low income and poor physical health.<sup>3</sup> Misuse of alcohol and illicit substances is common among people with schizophrenia.<sup>4,5</sup> All these factors contribute to high rates of depression in people with schizophrenia.

Around a quarter of people with schizophrenia meet criteria for a depressive disorder at some time in their lives.<sup>6</sup> However, many more people with schizophrenia experience subthreshold depressive symptoms. In the recent Australian Survey of High Impact Psychosis, people with a psychotic illness had high rates of depressed mood (79.6% at some time in their life and 54.5% in the previous year).<sup>3</sup> Depressive symptoms in schizophrenia may be associated with significant distress, particularly around themes of loss, grief and hopelessness, and can occur throughout all phases of the illness, including the prodrome, acute psychotic episodes and the post-psychotic phase. There is an increased risk of psychotic relapse when these symptoms persist in the chronic phase of schizophrenia.<sup>7</sup>

Suicide is about 13 times more likely in people with schizophrenia than in the general population.<sup>8</sup> Although the precise nature of the link between suicide and depressive symptoms in schizophrenia has not been firmly established,<sup>9</sup> depression remains the most significant mediator of suicide in the general population and this is likely to also pertain to people with schizophrenia. Hopelessness and demoralisation are indicators of increased risk of suicide, as are social isolation and substance use.

## The diagnostic problem

Despite increased vigilance and screening for depression in clinical settings, depressive symptoms in patients with schizophrenia are often either missed or dismissed by clinicians.<sup>10</sup> This is at least in part because of the difficulty of distinguishing between symptoms of a concurrent mood disorder and those of the schizophrenia syndrome itself, in which disturbed affect and difficulty expressing internal emotion are central negative symptoms. Further, differentiating schizophrenia with significant depressive symptoms from schizoaffective disorder and major depressive disorder with psychotic features (psychotic depression) can be difficult.

Depressive disorders in the setting of schizophrenia are inadequately characterised by current classification systems, such as the *Diagnostic and statistical manual of*

## Summary

- Depressive symptoms are common in people with schizophrenia and can be associated with suicidality, but are often either missed or dismissed by clinicians.
- General practitioners have a key role in initial assessment and subsequent monitoring of depressive symptoms, associated risks and physical health in patients with schizophrenia.
- Liaison with appropriate non-government organisations and public or private specialist mental health services can enhance GPs' management of depression in schizophrenia.
- Antidepressants, prescribed in tandem with antipsychotics, have a likely therapeutic role for persistent depressive symptoms in schizophrenia, but side effects can be troublesome.
- Although some of the atypical antipsychotics appear to have primary antidepressant effects, the utility of these agents alone in the setting of persistent depressive symptoms in schizophrenia has not been established.

*mental disorders, 4th edition, text revision (DSM-IV-TR).*<sup>11</sup> Specifically, the diagnosis of a comorbid mood disorder can only be made when the full set of criteria is fulfilled (eg, at least 2 weeks of unrelenting low mood for a major depressive episode). Also, the DSM-IV-TR allows for schizoaffective disorder to be diagnosed only when a full affective syndrome such as a major depressive, manic or mixed episode is present, as well as the patient manifesting, at a different time, Criterion A symptoms for schizophrenia (psychotic symptoms) in the absence of a full affective episode. On the other hand, according to the DSM-IV-TR, post-psychotic depressive disorder can be diagnosed only if a major depressive episode occurs in the residual phase of schizophrenia.

## Assessment

General practitioners have a key role in initial assessment and subsequent monitoring of depressive symptoms in patients with schizophrenia. Although depressive symptoms and negative symptoms of schizophrenia may appear similar, some features can help in differentiating them (Box). Primary negative symptoms of schizophrenia include apathetic withdrawal, restriction of affect and paucity of thought. Negative symptoms that are secondary to depressive symptoms may present in a similar fashion.

People with both schizophrenia and depression may have difficulty communicating a depressed mood or inner feeling state, thus limiting the clinical utility of direct questioning about their mood. Rather, questions about their interest in things and activities may be more useful in differentiating depressive symptoms. For example, a loss of interest in usual activities (anhedonia) is common in

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**Features differentiating negative from depressive symptoms<sup>10</sup>**

## Negative

- Blunted affect

## Depressive

- Prominent low mood
- Hopelessness, helplessness, worthlessness
- Guilt
- Suicidal ideation

contributors. Depressive symptoms may be a harbinger of general medical issues such as thyroid dysfunction or malignancy. Poor diet might be associated with anaemia, another potential cause of depressive symptoms. Obstructive sleep apnoea can also perpetuate fatigue and depression. Prescribed psychotropics or medications for other medical conditions (eg, antihypertensives or antibiotics) might also precipitate and perpetuate factors for depressive symptoms. On-referral for specialist evaluation might be appropriate; for example, referral to a respiratory specialist for evaluation and treatment of sleep apnoea, or to an endocrinologist if endocrine problems are suspected. Addiction medicine specialists can assist with substance misuse problems.

**Psychological treatment**

Most studies of psychological treatments for depression in schizophrenia have examined depression as a secondary or tertiary outcome measure and have generally not used well validated measures of mood, thereby limiting the evidence base.<sup>12</sup> The Schizophrenia Patient Outcomes Research Team guidelines<sup>13</sup> did not conclude effectiveness for any specific type of psychotherapy approach for depression in people with schizophrenia. However, a more recent Cochrane review suggested that cognitive behaviour therapy may be better than other psychosocial treatments for depressive symptoms in this context.<sup>14</sup> This is clearly an area where further research is required.

Demoralisation, with feelings of hopelessness, helplessness, an external locus of control, and lowered self-esteem, can be a component of comorbid depression in people with schizophrenia. It needs particular interventions, including meaning-based, cognitive behaviour, interpersonal and family therapies, as clinically appropriate.<sup>15</sup>

**Pharmacological treatment**

The literature on the efficacy of pharmacological interventions for depression in schizophrenia is modest. Methodological limitations have included: low power; severe depression, suicidality and substance use being exclusion criteria for trials; use of measures for depressive symptoms that are not ideal for people with schizophrenia; confounding from medication effects on sleep and appetite; and an absence of statistical techniques to assess the impact of reduced psychotic and extrapyramidal symptoms on mood.

Differentiating between depressive symptoms during an acute psychotic episode and depression in a stabilised patient after an acute episode is very important for treatment. Use of antidepressants in an acute psychotic episode may not help and may worsen psychotic symptoms, especially when antipsychotic treatment is not optimal.

**Antidepressants**

Most of the studies evaluating antidepressants in schizophrenia have been short-term. Siris and Bench identified 13 randomised controlled trials (RCTs) where antidepressants were added to antipsychotics.<sup>16</sup> Most used tricyclic antidepressants, and two used a selective serotonin reuptake inhibitor (SSRI). Only four trials were

depression. In contrast, patients with negative symptoms of schizophrenia alone ("deficit" syndrome) may describe their interests in a bland and affectively restricted manner.

Eliciting feelings of guilt or hopelessness and suicidal themes and ideation may also assist in differentiation, and in evaluating risk of self-harm or suicide. Other features of depression include significant neurovegetative symptoms, such as poor sleep and appetite change, but in schizophrenia, circadian rhythms and appetite may be affected by the core disorder and some antipsychotic medications.

Risk assessment is crucial for anyone with schizophrenia and depressive symptoms, as suicide is a leading cause of death among people with schizophrenia. Other risks such as self-neglect and poor oral intake must also be assessed, as many people with schizophrenia are socially isolated and do not have carers providing support or monitoring their wellbeing.

**Management**

GPs can take a central role in managing depression in patients with schizophrenia, but the involvement of other health professionals can assist in this process. General interventions should include psychoeducation, supportive psychological treatment (active listening, assistance with problem solving, and adaptively addressing stressors), encouragement to adhere to prescribed medication regimens, addressing broader psychosocial issues, and involving family and carers when appropriate. The GP can provide continuity of care while also seeking input from specialist mental health services. The latter is critical if there are concerns about the severity and persistence of symptoms, impaired functioning (eg, self-care, work, interpersonal), housing difficulties, limited engagement with or withdrawal from care, or risk of self-harm. Referral to and liaison with non-government sector agencies to assist with recovery-focused care can be very helpful for the individual.

Private-sector psychiatrists and psychologists (accessible via the Better Access initiative or private health insurance) can fulfil specific roles, such as providing expert medication management and focused psychological therapies, respectively. In rural regions, Medicare can also support access to specialist consultation via case conferences or teleconferencing.

In patients with schizophrenia and clear depressive symptoms, GPs have an important role in determining whether substance use (alcohol, illicit or prescribed medications) or general medical factors might be

positive on the primary outcome measure. A Cochrane review evaluating 11 RCTs involving 470 patients with schizophrenia and depressive symptoms concluded that there was no solid evidence to either support or refute the use of antidepressants in this context.<sup>17</sup> This review also reported some evidence for a beneficial effect of antidepressants on global functioning in depressed individuals with schizophrenia.

Other studies have assessed the impact of antidepressants on suicidality or suicide in schizophrenia. An RCT that added flexibly dosed citalopram (an SSRI) to antipsychotic medication for up to 12 weeks in middle-aged and older outpatients with schizophrenia found that there was a diminution of suicidal ideation, particularly in patients whose depressive symptoms abated with this treatment.<sup>18</sup> Moreover, a registry-based study found that antidepressant medication use in patients with schizophrenia was associated with a significant reduction in suicides.<sup>19</sup>

The weight of evidence is that antidepressants can play an important adjunctive role in treating depression in patients with schizophrenia, and may reduce suicide risk. Potential downsides include the complexity of the medication regimen, which may negatively affect adherence, and exacerbation of the side effects of prescribed antipsychotic medications (eg, SSRIs and serotonin–noradrenaline reuptake inhibitors can induce akathisia and sexual side effects, and mirtazapine can cause somnolence and weight gain).

### Antipsychotics

There are also few methodologically sound studies that have directly evaluated the effects of atypical antipsychotics on depression in people with schizophrenia. The non-pharmaceutical industry-sponsored Clinical Antipsychotic Trials of Intervention Effectiveness, involving 1460 patients with chronic schizophrenia, did not show any difference between the atypical antipsychotics and the typical comparator, perphenazine, on depressive symptoms.<sup>20</sup> A re-analysis of the European First Episode Schizophrenia Trial found that over the 1-year course of the study, there was no differential effect of atypical antipsychotics (olanzapine, quetiapine, amisulpride, ziprasidone) or low-dose haloperidol on depression, irrespective of whether concomitant antidepressants were used.<sup>21</sup> In clinical trials, the most consistent effects of atypical antipsychotics for treating depressive symptoms in schizophrenia have been reported for quetiapine<sup>22–24</sup> and olanzapine.<sup>25,26</sup> However, a Cochrane review concluded that there is no evidence to date that atypical antipsychotics are any better than typical antipsychotics, with or without antidepressant medication, for treating depression in people with schizophrenia.<sup>27</sup>

In terms of reducing suicidality, clozapine has been found to be beneficial in observational<sup>28</sup> and case register studies<sup>29</sup> and in a comparison with olanzapine.<sup>30</sup> While the exact mechanism of clozapine's antisuicidal effect is not known, the amelioration of depressed mood is thought to be significant.

### Conclusions

Significant depressive features are common in schizophrenia and are often intertwined with core psychotic symptoms, as well as being a significant mediator of disability and potentially driving suicidality. Best practice requires that the presence of depressive symptoms in patients with schizophrenia be thoroughly evaluated.

Despite the limitations of the evidence base, antidepressants, prescribed in tandem with antipsychotic medications, have a likely therapeutic role in people with schizophrenia and persistent depressive symptoms. However, any side effects of such medication combinations need to be balanced against therapeutic effects.

Although some of the atypical antipsychotics appear to have primary antidepressant effects, the utility of these agents alone in the setting of persistent depressive symptoms in schizophrenia has not been established. Psychological therapies such as cognitive behaviour therapy may have a role in treating depression in patients with schizophrenia. Strategies to overcome broader social problems are also required to help alleviate the burden of depression in people with schizophrenia and to instil hope for recovery.

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