Treating Depression in Schizophrenia

Prevalence and Consequences of Depressive Symptoms in Schizophrenia

Affective symptoms are common in schizophrenia; depressive symptoms are reported in as many as 80% of patients with schizophrenia. Symptoms of affective illness are sometimes reported in as many as 20% of individuals with schizophrenia. In addition to those who meet criteria for major depression, there are also a significant number of patients with schizophrenia who experience subthreshold depressive symptoms. Depressive symptoms in patients with schizophrenia can have devastating consequences including increased rates of psychiatric relapse and hospitalization, worse social functioning and cognitive symptoms, increased risk for suicide attempt, and worse quality of life.

Psychotic symptoms such as delusions and hallucinations that are prominent affective symptoms. Depressive symptoms significantly increase the risk of suicide. In a majority (80%) of patients with schizophrenia/hyponotice depression while experiencing depressive symptoms. Similarly, suicide attempts are even more common in patients with schizophrenia with antidepressant disorder compared to those with schizophrenia or a mood disorder. Interestingly, suicide risk has not been associated with either positive or negative symptom domains.

Schizoaffective Disorder

Depressive symptoms in schizophrenia can present as schizoaffective disorder, comorbid depression, or as subthreshold depression in which depressive symptoms do not meet criteria for major depression. Schizoaffective disorder is described as schizophrenia in which the patient also meets criteria for a mood disorder (major depressive episode) and manic episode. The diagnostic criteria for schizoaffective disorder also require that psychotic symptoms are present without prominent most symptoms for at least 2 weeks.

Comorbid and Subsyndromal Depression

Comorbid and subthreshold depression can occur before, during, or after a psychotic episode. In fact, depressive symptoms can be a sign of imminent psychiatric relapse in many patients. Affective symptoms are among the most prevalent prodromal signs with an accuracy as high as 85% of patients suffering a depressive mood in the weeks leading up to a first hospitalization for psychosis. In patients at risk for developing schizophrenia, symptoms of depression and anxiety may predict higher risk for the subsequent development of psychosis and higher severity of first-episode psychosis. In this context, symptoms of depression and anxiety may serve as vulnerability markers in individuals at risk for developing schizophrenia. Depressive symptoms that occur during a psychotic episode are often amenable to treatment. Postpsychotic depression, occurring after a psychotic episode, may persist and worsen in some patients after a psychotic episode are often amenable to treatment. Post-psychotic depression, the ventromedial prefrontal cortex (VMPFC). Additional blockade of serotonin 5HT2A receptors, atypical antipsychotics also bind to serotonin 5HT2A receptors. Aripiprazole, an SGA with D2/D3 partial agonist activity, has been shown to improve depression. Additionally, the actions of D2/D3 partial agonists have antidepressant and anorectic effects due to not antipsychotic activity of overstimulation D2/D3 receptors.

Enhancement of norepinephrine neurotransmission in the PFC, via norepinephrine reuptake inhibition (NRI) is another proposed mechanism for antidepressant activities of antipsychotics. Both ipratropium and oxathine (via its active metabolite norquetiapine) may exert antidepressant effects in part through this mechanism of enhanced norepinephrine neurotransmission. Ziprasidone has the additional property of serotonin reuptake inhibition (SRI) which may also contribute antidepressant effects by increasing serotonergic neurotransmission.

Antidepressant at serotonin 5HT2C receptors, a property shared by many SGAs, may also have an antidepressant effect through disinhibition of dopamine and norepinephrine release in the prefrontal cortex (PFC). SGAs with 5HT2C antagonistic activities include clozapine, olanzapine, and quetiapine.

Symptoms of depression in schizophrenia can have devastating consequences including increased risk for suicide attempt, and worse quality of life. There are no consistent recommendations as to how schizoaffective disorder or depressive symptoms in schizophrenia are most effectively treated. Despite this fact, antidepressants and/or mood stabilizers are often used in conjunction with antipsychotics for the treatment of schizophrenia. The 1999 Expert Consensus Guidelines recommend treatment of schizophrenia and comorbidity depression with atypical drugs of SGAs, followed by augmentation with an SNRI. Treatment is often initiated with optimal doses of SGAs, followed by augmentation with an SSRI, followed by augmentation with an MAOI. More recent guidelines have indicated that there are not enough data on which to base a recommendation for the treatment of depressive symptoms in schizophrenia.

Aripiprazole

Aripiprazole, an atypical antipsychotic with D2/D3 partial agonist activity, has been shown to improve depression. Additionally, the actions of D2/D3 partial agonists have antidepressant and anorectic effects due to not antipsychotic activity of overstimulation D2/D3 receptors.

Figure 1. Dopaminergic Circuits in Schizophrenia and Depression

By function or various neurotransmitter systems as hyperactive (A) or hypoactive (B) the symptoms of schizophrenia. (A) Hyperactive dopamine systems in the mesolimbic system underlie the positive symptoms of schizophrenia. B) Hypoactive dopaminergic and serotonergic subcortical pathways. Hyperdopaminergia in the ventromedial prefrontal cortex may contribute to the negative and cognitive symptoms of schizophrenia. C) The monoamine hypothesis of depression proposes that depressive symptoms may be due to hypodopaminergia in the cortex and may contribute antidepressant effects by increasing serotonergic neurotransmission. D) Additional binding properties of some SGAs that lead to increased dopamine, norepinephrine, and serotonin activity in the same brain region. Antipsychotics exacerbate the symptoms caused by hypodopaminergia in the cortex.

Figure 2. Antipsychotics and Affective Symptoms

A) Unlike conventional antipsychotics, atypical antipsychotics are also antipsychotics. Aripiprazole also binds to serotonin 5HT2A receptors, atypical antipsychotics also bind to serotonin 5HT2A receptors. B) In the mesolimbic pathway, binding of serotonin 5HT2A receptors to SGAs is hypothesized to cause a change in hypodopaminergic symptoms. C) Conversion to antidepressant symptoms is hypothesized to cause a change in serotonin activity in the cortex. Additional blockade of serotonin 5HT2A receptors by atypical antipsychotics may help ameliorate some of the symptoms caused by hypodopaminergia in the cortex.

The Neurobiology of Depression in Schizophrenia

Ultimately, the expression of depression is largely due to dysfunction of neurotransmitter systems (Fig. 1). It may be that the disruption of one system (e.g. dopamine) underlies depression in a patient. The disruption of another neurotransmitter system (e.g. serotonin) that underlies the expression of affective symptoms. Alternatively, there may be a common genetically predisposing factor (e.g. catechol-o-methyltransferase; COMT) or process (e.g. energy metabolism) that leads to dysfunction of multiple systems simultaneously.

Treatment with medications that block dopamine D2 receptors (i.e. antipsychotics) may induce affective and negative symptoms by exacerbating a hypodopaminergic state in the ventromedial prefrontal cortex (VMPFC). Additional blockade of serotonin SHT2A receptors by atypical antipsychotics is hypothesized to increase affective, negative, and cognitive symptoms caused by excessive D2 antagonism in the cortex (Fig. 2).

Figure 3. Dopaminergic Pathways: SHT2A and VMPFC

A) Mesocortical Pathway in SHT2A and VMPFC. B) Mesocortical Pathway in SHT2A and VMPFC.