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DEPRESSION IN SCHIZOPHRENIA – LITERATURE OVERVIEW

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Epidemiology

Estimates of the prevalence rate of the depression syndrome in patients with schizophrenia range from 7% to 78% with the an average around 25% (Siris 2001, Sands 1999, McGlashan 1976). Studies have varied considerably in terms of the definitions employed for schizophrenia and depression, differences in cohort status, the observed interval, illness chronicity, assessment methodology, and patient status. Depression during the acute phase of schizophrenia may be associated with a favorable course and outcome (Stephens 1966), but several studies have suggested that depression during the chronic phase of schizophrenia has negative impact on the course of the illness (Siris 1991, Siris 2000, Conley 2007, Falloon 1978). It is associated with a greater risk of suicide and relapse (Caldwell 1990, Fenton 1997). Depression may occur independently of the symptoms of schizophrenia and several months after recovery from an acute episode, i.e. post-psychotic depression, in up to 30% of cases (Siris 1995); it is known to be both a precursor and a concomitant feature of hopelessness and suicidal thinking (Drake 1986, Pompili 2007). The emergence of affective symptoms may represent a psychological reaction to impending relapse, may reflect an underlying biological process mediating both these symptoms and positive psychotic symptoms, or may be an epiphenomenon (Birchwood 2000).

The stress-vulnerability model

The stress-vulnerability model has potential as an integrating concept concerning the relationship between depression and psychosis. The stress-diathesis model of schizophrenia depicts the psychosis of schizophrenia as a final common pathway of neuropsychiatric decompensation (Zubin 1977). Psychosis is viewed as multi-factorial, and results from an interaction of a predisposing vulnerability (of biopsychosocial origin) with environmental stressors. The vulnerability factors include emotional difficulties, such as low self-esteem and social anxiety, cognitive biases or deficits, emotions, connected to stigma due to schizophrenia, and biological factors of genetic and neuro-developmental origin. Stresses might bring on the illness or relapse. The stressors, such as stressful life events, hostile environments, psychoactive drugs or prolonged social isolation, affect both the cognitive and emotional processes of the vulnerable individual, causing changes such as anxiety or depression, and information processing difficulties and resulting anomalous experiences (e.g. hallucinatory experiences). These changes are disturbing and are actively interpreted by the individual; the resulting interpretations of the meaning of these changes to the self and of the triggering events lead to the fully formed psychotic symptoms. Similar processes then maintain the psychosis and, in addition, the experience and consequences of psychosis itself and its treatment may provide further maintaining factors, such as a reluctance to take medication or depressed mood and hopelessness (Siris 2000, Koreen 1993).

Clinical course

Depression is an important and heterogenous clinical syndrome, which may may occur at any time during the course of the illness. Depression can follow the same course as positive symptoms and present *de novo* during follow-up without a change in positive symptoms (Siris 2000, Mulholland 2000). Birchwood suggests a distinction between three core (but not mutually exclusive) pathways: emotional disorder that is intrinsic to the psychosis diathesis, a psychological reaction to it, or the product of disturbed developmental pathways (Birchwood 2000). The depression syndrome is a complex of features that typically involves the symptom of depression but

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also includes cognitive and vegetative features such as pessimism, guilt, impaired concentration, lack of confidence, loss of interest or pleasure, and disturbances in sleep, appetite, and energy level (Siris 1991).

Depression as a prodromal syndrome

Depression is nearly always part of the first-episode prodrome that recedes with the positive symptoms (Birchwood 2000). The second generation of factor analytical studies of psychotic symptoms yield an additional dimension of depressive symptoms alongside the positive and negative dimensions (Stefanis 2002). The symptoms most frequently mentioned by patients and their families were: "symptoms of dysphoria that non-psychotic individuals experience under stress, such as eating less, having trouble concentrating, having trouble sleeping, depression and seeing friends less" (Herz 1980). Some early psychotic symptoms can co-occur. Depression as a prodromal syndrome usually lasts for several weeks. Treatment with antipsychotics helps to reduce depressive symptoms. The therapeutic implications of this pathway to emotional disorder lie in the treatment of core psychotic symptoms.

Depressive symptoms during acute episodes

Depressive symptoms are most frequently associated with the acute phase of the illness. Such symptoms are most prevalent before medication is commenced (Knights 1981). They occur in more than half of first-episode or drug-free patients (Johnson 1981). The prevalence of depressive symptoms falls dramatically during the course of an admission for an acute relapse, and occurs in approximately 25% of patients during the six months following discharge. The close association between depressive symptoms and acute episodes adds weight to the hypotheses that such symptoms are a core feature of schizophrenia and suggests that depressive symptoms and more typically schizophrenic symptoms may share common pathophysiological processes (Siris 2000, Birchwood 2000). Newly emerging affective symptoms are a useful early warning sign of impending relapse.

Depressive symptoms in chronic schizophrenia

Lower rates of depressive symptoms are seen in the chronic phase of the illness. Most of the reported studies on chronic patients do not define the clinical stability or otherwise of the patients involved (Mulholland 2000). Persistent positive symptoms in the chronic phase of the illness may lead to distress, demoralisation and depression.

Reactions to Disappointment or Stress

Psychosis affects not only a person`s cognitive and emotional being but also self-identity. Ilness, traumatic experiences due to illness, etc are a heavy burden for patients, who very often experience a feeling of stigma. Reactions to disappointments, a sense of loss or powerlessness, or awareness of psychotic symptoms or psychological deficits can certainly present as or contribute to depression, especially when depression follows closely after a stressful event or exacerbation of schizophrenia (McGlashan 1976, Siris 2000, Birchwood 2000, Birchwood 1993, Liddle 1993, Lysaker 1995). Such reactions are of two types: acute and chronic. Acute reactions to disappointment or stress which are suggested by the parallel history of a recent compatible event are generally brief, lasting hours, days, or at most weeks, and may be responsive to supportive interventions or counterbalancing positive experiences. Chronic reactions to disappointment or stress have also been termed the demoralization syndrome and last longer (Frank 1973, Klein 1974, deFigueiredo 1993). Demoralization is important to diagnose because it may be more responsive than other depressed states to appropriately targeted psychosocial interventions (Siris 2000, Birchwood 1993).

Post-psychotic depression

The terms ‘post-psychotic depression’, ‘post-schizophrenic depression’ and ‘secondary depression’ have been used to describe the occurrence of depressive symptoms during the chronic phase of schizophrenia. The ICD-10 definition of post-psychotic depression (F20.4) requires that, along with the general criteria for schizophrenia during the previous 12 months, the patient must still exhibit persistent hallucinations, thought disorder or negative symptoms not due to depression or neuroleptic medication (WHO 1992). Patients, particularly those experiencing first-episode psychosis, need to be monitored for post-psychotic depression /hopelessness/suicide risk some weeks after the acute episode. It can be argued that the rise in depression during the post-psychotic depression phase may be an early sign of a further psychotic episode, because dysphoria is a known precursor of psychotic relapse (Birchwood 2000).

Differential diagnosis of depression in the course of schizophrenia

Differential diagnoses to consider include schizoaffective disorder, organic conditions and the negative symptoms of schizophrenia. It has been argued by some that depression may in some way be 'caused' by antipsychotic medication. Depression may also be an understandable psychological reaction to schizophrenia. When all of these possibilities have been excluded, there is evidence that depression is perhaps most often an integral part of the schizophrenic process itself.

Differentiating depressive from negative symptoms

The major difference between depression and negative symptoms in schizophrenia are 'blue mood' - prominent subjectively low mood and prominent blunting of affect. Lack of energy, anhedonia, alogia, affective flattening apathy and social withdrawal may cause problems when trying to differentiate between the two syndromes. In schizophrenia, the biological features of the depressive syndrome, such as insomnia and retardation, are not always present – and if they are present, they can be more difficult to disentangle from negative symptoms and can be an intrinsic part of the illness separate from any superimposed depressive syndrome (Siris 2000, Mulholland 2000).

Schizoaffective Depression

Differentiating schizophrenia with clinically significant depressive symptoms from schizoaffective disorder is not always easy. According to ICD-10 schizoaffective depression has been defined differently according to various diagnostic schemes, which has resulted in variations in the boundary between schizoaffective depression and depression in schizophrenia (Siris 2000, WHO 1992). In DSM-IV, schizoaffective disorder refers to patients in whom a full affective syndrome coincides with the florid psychotic syndrome but who also have substantial periods of psychosis in the absence of an affective syndrome (American Psychiatric Association 1994).

Organic Conditions

Cardiovascular disorders, pulmonary infections, autoimmune diseases, anemia, cancer, and metabolic, neurological, and endocrine disorders can induce psychological symptoms directly in the person with schizophrenia, or depressive symptoms may occur as a reaction to illness. The medication used to treat medical disorders, such as ß blockers, other antihypertensive agents, sedative hypnotics, antineoplastics, barbiturates, nonsteroidal anti-inflammatory drugs, sulfonamides, and indomethacin can cause depression as a side effect. The discontinuation of other prescribed medications such as corticosteroids and psychostimulants can cause depression (Siris 2000, Mulholland 2000).

Treatment of depression in schizophrenia

Treatment of the non-psychotic dimensions of schizophrenia is a critical part of recovery. The therapeutic goal is significantly to reduce the excess morbidity and mortality associated with depressive symptoms. Early assessment which takes into consideration the stage of the illness, and the differential diagnosis of depressive symptoms in schizophrenia has an important impact for the outcome of psychosis. The treatment options are largely dictated by the stage of the illness. The first consideration concerning a newly emergent depressive reaction in schizophrenia is whether it is a transient reaction to disappointment or stress or the prodrome of a new psychotic episode (Siris 1991, Harrow 1994). A new onset of depression may be a potential early sign of psychotic relapse in schizophrenia. During acute episodes, depressive symptoms should not be treated separately from other symptoms and are likely to resolve as the episode resolves. In the majority of cases increased antipsychotic medication, increased psychosocial support and, if necessary, hospitalisation, will successfully treat depression as well as positive symptoms. Siris advocates responding to a new onset of depression with greater attention and psychosocial support and would consider adding an adjunctive antidepressant only if the depression syndrome becomes a stable feature in the absence of psychotic relapse (Siris 2000).

The new atypical antipsychotics are more efficacious in treating the depression associated with an acute episode (Resnick 2004, Kramer 1989, Tollefson 1999, Drake1986). The atypicals may prove to be useful for the depression that emerges during the chronic phase of the illness. Clozapine has been shown to reduce hopelessness, depression and suicidality in people with chronic schizophrenia (Kramer 1989).

There is a good case for the prescription of an antidepressant when the patient has persistent depressive symptoms and is not in a phase of acute

illness (Tollefson 1999). Selective serotonin reuptake inhibitors (SSRIs) have overall been successful in treating depressive symptoms in schizophrenia. Given the relative safety of SSRIs compared with the tricyclics, they would seem to be the antidepressants of choice. However, it is necessary to bear in mind possible pharmacokinetic interactions with antipsychotics because of the enzyme inhibitory effects of some of the SSRIs on the CYP450 system. A caveat with the tricyclics, however, is that occasionally there can be a worsening of the positive psychotic symptoms (Siris 2000).

Modern, placebo-controlled clinical trials in the 1980s did not find significant improvement in depressive symptoms in patients with schizophrenia given ECT, but did so in patients with psychotic symptoms (Cooper 1995).

Psychotherapy, rehabilitation, social support and work opportunities has been shown to be effective for the demoralisation seen in schizophrenia. Patients should have the opportunity to talk about their feelings connected with the illness, their traumatic experiences and stigma due to mental illness. A person`s recovery from psychosis is possible and involves more than a reduction of symptoms. It involves the entire self, bringing all components of physical, emotional, mental and spiritual aspects of themselves into their experience of life. For this recovery to be successful, it needs the full involvement of healthcare providers. Active listening and communication in a consistent setting are necessary when providing assistance to patients experiencing recovery from psychosis (Birchwood 1993).

It is important to exclude cases of schizoaffective disorder and any medical conditions that are present and to treat them appropriately. The possibility of substance misuse as a contributing factor has to be excluded. Akathisia should always be considered and managed in patients describing feelings of depression. If antipsychotic medication is producing akinesia, its dose should be reduced and /or the anticholinergic medication should be introduced in therapy. Use of an anticholinergic drug is generally effective. Other options include ß-adrenoceptor antagonists, a benzodiazapine or a change in antipsychotic drug (De Nayer 2003). Negative symptoms should be excluded and treated appropriately.

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