

## Review article

# Differential diagnosis of depressed mood in patients with schizophrenia: a diagnostic algorithm based on a review

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**Objective:** To review the available literature on depressive symptomatology in schizophrenia in order to establish a diagnostic algorithm of depressive syndromes in schizophrenia.

**Method:** A literature search was performed using PubMed and Medline. Additional information was gained by cross-referencing from papers found in the database. Data from controlled studies as well as supplementary information from review articles and psychiatric manuals pertinent to the topic were used. Depressive symptoms were classified with respect to their temporal relationship to acute psychotic symptoms before the background of nosological entities as operationalized by Diagnostic Statistical Manual IV (DSM IV).

**Results:** Depression is a common and devastating comorbid syndrome in patients suffering from schizophrenic disorder. The paper summarizes the relevant diagnostic steps to guide the clinician towards therapeutic interventions, which differ depending on the nature of the depressive syndrome.

**Conclusion:** Differentiating depressive states in schizophrenia has consequences in terms of choosing therapeutic strategies. An algorithm which leads the practitioner to a reliable diagnosis and in consequence to a valid therapy is presented.

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## Introduction

Depression is a common comorbid syndrome in patients suffering from schizophrenic disorder. Prevalence studies report widely varying numbers ranging from a low of 7 (1) to 30% (2, 3) and 33% (4) up to 75% (5). A recent paper (6) identified 52% in acute psychotic patients and 38% during more stable periods of the disease. Lifetime prevalence in patients with schizophrenia was reported to be 60 (2, 7, 8) up to 80% (9, 10). This is a significant risk, when compared with a lifetime incidence of depression of 8–26% in the general population (11).

Depressive symptoms in patients with schizophrenia were already reported in the first descriptions of the syndrome (12, 13). Many psychiatrists believed that the advent of depression along the

course of schizophrenia is a good prognostic sign. Some research and more recent findings have supported this view (14–17). Most studies, however, found that the advent of depression along the course of the illness is associated with an increased rate of relapse (18, 19), more frequent and longer duration of hospitalizations (20–22) and poor response to pharmacological treatments (23). Cognitive impairment (24, 25), poor social functioning (26–30), substance abuse (31–33), negative attributional style (34) and suicide/suicide attempts (9, 22, 35–39) have also been reported. Compared with patients who had not attempted suicide, patients with a history of suicide attempts had a greater number of lifetime depressive episodes and an earlier age of onset (40) although these findings are not uncontested (41).

There is an ongoing discussion concerning the classification of depression in schizophrenia. Many research groups have reported studies showing that depressive symptoms are regular features of schizophrenia, seen most frequently during the acute florid phase of the illness and gradually becoming less prevalent during remission (5, 21, 42–47). These authors have concluded that the association between depressive and positive symptoms points to a specific relationship between affective symptoms and the positive symptom domain of schizophrenia. Knights and Hirsch (42) have coined the term ‘revealed depression’ to describe an unmasking of depression through fading out of psychotic symptomatology. Other authors view ‘post-psychotic depression’ as being a heterogeneous group of disorders of different etiologies (48–50).

Even if depression is a part of the schizophrenic syndrome, not all depressive symptoms must necessarily be related to the core symptomatology (21). They may occur as a subjective reaction to the experience of psychotic decompensation (5). On the other hand, Subotnic and coworkers (51) have found that depression in schizophrenia correlates with a positive family history for depression indicating a genetic liability. Conversely, recent findings on a shared genetic liability between depression and schizophrenia are questioning the concept of genetic monocausality (52). It has been suggested that a broad phenotype, including unipolar depression, bipolar disorder, schizoaffective disorder and schizophrenia, when accompanied by significant affective symptoms, can result from mutations within a gene in a specific chromosomal region (53), but the concept of a causative gene is being replaced by a more complex paradigm in which gene-interactions in concert with non-genetic factors lead to symptomatology (54). This concept is well known as the stress-vulnerability model. This model presumes a genetic vulnerability to schizophrenic psychosis, which is clinically apparent if triggered by a stressor (55–57). Siris (50) argues that depression could be such a stressor which is strong enough to induce a psychotic relapse. This assumption would also explain why depression as a prodromal symptom leads to psychosis.

The discussion of a nosological differentiation of depression in schizophrenia becomes futile, if depression is not recognized. New data suggest that US psychiatrists identify depressive symptoms in about one-third of their patients, but that a quarter of these specialists rarely prescribe adjunctive antidepressant medication (58). Recognition and treatment of depressive symptoms, therefore, still remains a challenge in everyday clinical prac-

tice. This was the reason why we propose, based on a literature search, an algorithm in order to simplify differential diagnosis and in consequence adequate therapy (Fig. 1). This algorithm albeit based on the available evidence has yet to be formally studied.

### Material and methods

In order to obtain data concerning depression in schizophrenia, we performed a literature search using PubMed and Medline. We entered the keywords schizophrenia and depression and found 5057 references. Data from controlled studies as well as supplementary information from review articles and psychiatric manuals pertinent to the topic were used. Additional information was gained by cross-referencing from papers found in the database. Altogether, we report on 153 articles dealing with depression in schizophrenia. These articles were published between 1908 and 2002 with a focus on papers published since 1997. Most of the reviewed reports are original studies dealing with the phenomenology, prevalence, nature or treatment of depression in schizophrenia. Twelve papers are review articles.

In order to establish a clinically relevant algorithm, depressive symptoms were classified with respect to etiology and their temporal relationship to acute psychotic symptoms before the background of nosological entities as operationalized by Diagnostic Statistical Manual IV (DSM IV).

#### Secondary (organic) causes for depression

We refer to secondary causes for depression as causes because of underlying medical etiologies

*Drug induced depressive symptoms. Treatment related depressive symptoms:* One of the issues is still discussed controversially is whether or not antipsychotics induce depressive mood or predispose to depressive states in patients with schizophrenia. Johnson stated that a significant part of depression is not drug related, but that neuroleptics could play a role (7.5–12.5%) in the etiology of depression (21). In contrast, Hogarty and Munetz (59) as well as Hirsch and colleagues (60) have not found evidence of a potential depressiogenic effect of antipsychotics.

Antipsychotics, especially traditional compounds, may induce syndromes which mimic depression. Depressive-like states occur in association with the extrapyramidal side-effects of akinesia and akathisia. Neuroleptic-induced akinesia, a syndrome consisting of reduced motor activity with

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the characteristic appearance of hypomimia, may resemble the loss of affective responsiveness found in depression (61–63). The term ‘akinetic depression’ was coined by Van Putten and May for this syndrome (62). It includes a reduced level of activity as well as anhedonia, responding to anticholinergic medication. More recently, ‘secondary negative symptoms’ is commonly used to describe such adverse effects.

Neuroleptic-induced akathisia is easy to diagnose if it emerges in its typical phenomenology (63). Diagnostic difficulties occur when one is confronted with its abortive form, where patients exert more signs of dysphoria than motor restlessness. This may be mistaken for agitated depression and both suicidal ideation and behavior have been associated with it (64). The Hillside

Akathisia Scale (65) in concert with the Calgary Depression Scale (CDS) may help to establish a valid diagnosis.

Adjustment of medication may also help to clarify diagnostic uncertainty. If patient’s mood improves with a dose increase of antipsychotic medication, depression is more likely to be related to the primary disease process of schizophrenia. In patients who improve with dose reduction, the diagnosis may be secondary negative symptoms. Some clinicians use an anticholinergic challenge to rule out EPS, before making the diagnosis of depression (50).

Sedation because of tranquilizers or the sedative effect of neuroleptics may also be confounded with depression at the first glance. The fatigue and orthostatic dysregulation some low potency neu-

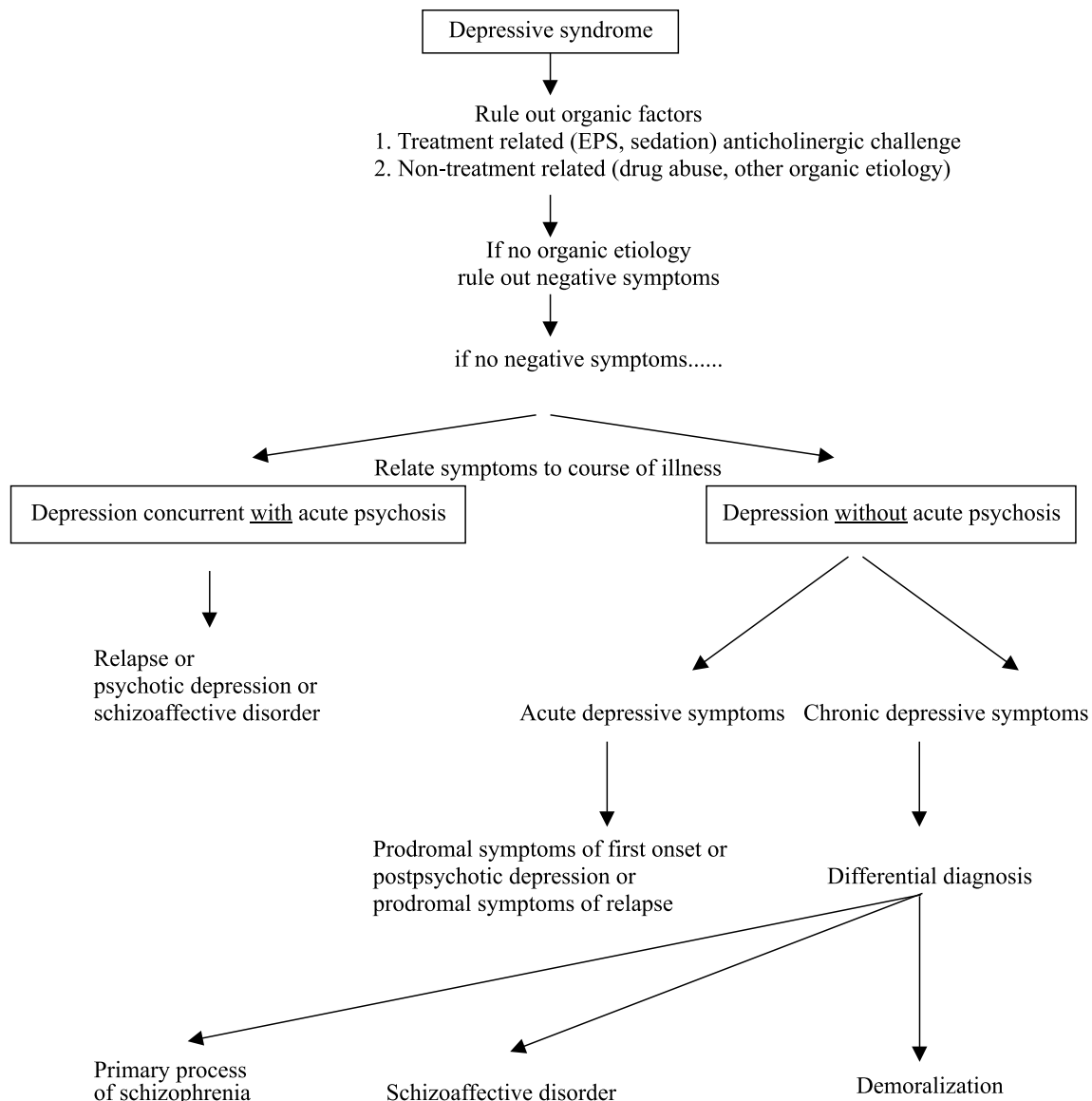


Fig. 1. Diagnostic algorithm of depressive syndromes in schizophrenia.

Table 1. Characteristics and results of selected studies of depression in schizophrenia

Authors	Study characterization	n	Diagnosis	Tools	Main results
Falloon et al. (1978) (20)	Longtime comparison of fluphenazine vs. pimozide	53	Schizophrenia	PSE	Depression positively correlated with psychotic relapse
Knights et al. (1981) (42)	Comparison of depression in three groups: acute vs. stable symptoms vs. patients with monopolar depression	37	Schizophrenia	PSE	Depressive symptoms in acute schizophrenia decrease after
		62	Schizophrenia	BDI	effective neuroleptic treatment
Johnson (1981) (8)	Longitudinal assessment of depressive symptoms over a period of 8 years	37	Schizophrenia	BPRS EPRS	A significant part of depression in schizophrenia is not drug related
Möller and von Zerssen (1982) (43)	Analysis of frequency and course of depression during hospitalization	67	Schizophrenia	IMPS	Neuroleptics are unlikely to be the major cause for depression
Hogarty and Munez (1984) (69)	Double blind study in which non-depressed, non-relapsed patients were randomized to treatment with chlorpromazine or placebo	NA	Schizophrenia	CSRS NA	Chlorpromazine did not contribute to the genesis of depression
Martin et al. (1985) (7)	Cross-sectional study at two time points	500	Schizophrenia	NA	Nearly 60% of patients suffer from a depressive episode along the course of the illness
Elk et al. (1986) (3)	Cross-sectional study in acute psychotic patients of different ethnic background	56	Schizophrenia	PSE	Depression was found in 30% of patients
Johnson (1988) (2)	Prospective monitoring	119	Schizophrenia	CGI BPRS HDRS	Depression after 1 years of recovery indicates an increased risk of acute relapse within 2 years
Hirsch and Jolley (1989) (1)	Double blind randomized comparison of fluphenazine and placebo in stable patients with schizophrenia	54	Schizophrenia	BDI ESQ SCL-90	Significantly more patients in the placebo group experienced dysphoric episodes compared with the fluphenazine group
		194	Schizophrenia	PSE MADRS BDI SANS CPRS EPRS BAS	In the detected (13%) patients with depression it was not related to medication
Kramer et al. (1989) (90)	Cross-sectional study of clinical characteristics in chronic in-patients	58	Schizophrenia	BPRS HDRS	Adjunctive antidepressants are not indicated for the treatment of depression in actively psychotic in-patients
Newcomer et al. (1990) (147)	Double blind study comparing haloperidol/tricyclics to haloperidol/placebo	69	Schizophrenia	HDRS BPRS	Negative and depressive symptoms can be assessed independently
Addington and Addington (1992) (22)	Cross-sectional analysis of depression and negative symptoms in unmedicated patients	50	Schizophrenia	NA	Suicide attempts significantly correlated with depression on admission and after 6 months

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Table 1. (Continued)

Authors	Study characterization	n	Diagnosis	Tools	Main results
Kibel et al. (1993) (126)	Cross-sectional study attempting to differentiate affective and negative symptoms	73	Schizophrenia	SANS NSRS PANSS MSS MADRS KS HDRS	Depressive and negative symptoms can be reliably distinguished and measured
Koreen et al. (1993) (5)	Longitudinal study in first episode patients in order to determine prevalence and prognostic significance of depression	70	Schizophrenia		Most depressive symptoms resolved as the psychosis remitted antidepressant should only be given to patients with persistent depression
Nakaya et al. (1997) (45)	Prospective and longitudinal assessment of depressive, negative, and positive symptoms	86	Schizophrenia	HDRS PANSS EPRS AIMS NA	Improvement of depressive symptoms correlated with the improvement in positive symptoms
Subotnik et al. (1997) (51)	One year follow up investigating depression in patients with schizophrenia in relation to familial risk	70	Schizophrenia		Depression in patients with schizophrenia was associated with family history of unipolar depression
Kohler et al. (1998) (24)	Cross-sectional study to elucidate the etiology of depression in schizophrenia by grouping patients with depression into a groups of high depression and low depression	63 81	Schizophrenia	HDRS	Association between attentional impairment and depression is consistent with frontal lobe dysfunction
Gupta et al. (1998) (40)	Study exploring the association between psychosocial variables in patients who attempted suicide in comparison with patients who did not	336	Schizophrenia Schizoaffective disorder	NA	Patients with suicide attempts had a greater number of lifetime depressive episodes compared with patients without attempts
Holthausen et al. (1999) (25)	Cross-sectional study in recent onset patients investigating cognitive deficits, depression and schizophrenia	50	Schizophrenia	PANSS	Depression showed a correlation to objective and subjective cognitive measures like simple and divided attention, etc.
Emsley et al. (1999) (17)	Longitudinal survey over a 7-year period	177	Schizophrenia schizophreniform disorder	PANSS-D	Depressive and positive symptoms were correlated. Depressive symptoms may predict better outcome
Sands and Harrow (1999) (19)	Prospective study to assess depression in schizophrenia, major depression and schizoaffective disorder	70 31 17 69	Schizophrenia Schizoaffective Psychotic depression Non-psychotic depression Schizophrenia	RDC SADS	Poorer post-hospital adjustment in patients with schizophrenia
Zisook et al. (1999) (46)	Cross-sectional study of patients with schizophrenia without major depression	60	Schizophrenia	HDRS PANSS	Severity of depressive symptoms correlated with that of positive symptoms. Depression may be an independent core component of schizophrenia
Shah and Ganesvaran (1999) (38)	Post hoc analysis of 62 suicides	62	Schizophrenia	NA	Suicide was associated with greater number of episodes, greater number of neuroleptics and antidepressants

Table 1. (Continued)

Authors	Study characterization	n	Diagnosis	Tools	Main results
Wassink et al. (1999) (4)	Prospective study over 5 years	70	Schizophrenia	NA	Depression is common in early schizophrenia
Moore et al. (1999) (121)	Cross-sectional assessment of depression and level of insight into the disease	46	Schizophrenia	CDS BDI	Depression is related to the level of insight into the disease
Haefner et al. (1999) (28)	Retrospective assessment of 232 first episode patients and prospective assessment of 115 patients	232 115	Schizophrenia	NA	A total of 73% showed a prodromal phase of several years. Depression and negative symptoms were first symptoms
Harkavy-Friedmann et al. (1999) (41)	Cross-sectional assessment of clinical characteristics within two groups of patients, one with the other without attempted suicide	156	Schizophrenia Schizoaffective disorder	DIGS	Individuals with or without suicide attempts did not differ in terms of rate of depression
Bottlender et al. (2000) (39)	Prospective assessment of depression in first admitted patients	998	Schizophrenia	GAS AMDP	Depressed patients with schizophrenia were more likely to have suicidal tendencies
Baynes et al. (2000) (44)	Study of prevalence and correlates of depression	120	Schizophrenia	BDI BPRS HDRS CGI ESRS BAS SOS	Depressive symptoms in stable patients with schizophrenia are related to the degree of persistent positive psychotic symptoms
Lancon et al. (2001) (6)	Prospective comparison between two rating scales	68	Schizophrenia	CDS PANSS	Relationship between depression and other symptoms of schizophrenia seems to differ during different stages of the illness

AIMS: Abnormal Involuntary Movement Scale (NIMH 1974); AMDP: Association for Methodology and Documentation in Psychiatry (Pietzger et al. 1983); BAS: Barnes Akathisia Scale (Barnes 1989); BDI: Beck Depression Inventory (Beck et al. 1961); BPRS: Brief Psychiatric Rating Scale (Overall and Gorham 1962); CDS: Calgary Depression Scale for Schizophrenia (Addington et al. 1990); CGI: Clinical Global Impression (Guy 1976); CPRS: Comprehensive Psychiatric Rating Scale (Asberg 1978); CSRS: Clinical Self Rating Scales (von Zerssen 1976); DIGS: Diagnostic Interview for Genetic Studies; EPRS: Simpson and Angus Extrapyramidal Psychiatric Rating Scale (Simpson et al. 1964); ESO: Early Signs Questionnaire (Herz et al. 1982); GAS: Global Assessment Scale (Endicott et al. 1976); HDRS: Hamilton Depression Rating Scale (Hamilton 1960); IMPS: In-patient Multidimensional Psychiatric Scale (Lorr and Klett 1974); IRAOS: Interview for the Retrospective Assessment of the Onset of Schizophrenia (Häfner et al. 1990); KS: Krawiecka Scale (Krawiecka et al. 1977); MADRS: Montgomery-Asberg Depression Rating Scale (Montgomery-Asberg 1979); MRC: Social Performance Schedule (Stevens 1972); MSS: Montgomery Schizophrenia Scale (Montgomery and Taylor 1978); NA: Not assessed; PANSS-D: Depression Subscale of the Positive and Negative Syndrome Scale (Kay et al. 1987); PSE: Present State Examination (Wing et al. 1974); RDC: Research diagnostic criteria (Spitzer et al. 1978); SADS: Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer 1978); SANS: Scale for the Assessment of Negative Symptoms (Andreasen 1981); SCL-90: Symptom Check List (Derogatis et al. 1973); SOS: Significant Others Scale (Power et al. 1988).

roleptics induce can contribute to the diversity of pseudo-depressive states.

On the other hand, some of the newer antipsychotics like zotepine (66–68) or ziprasidone (69, 70) are norepinephrine and/or serotonin reuptake inhibitors, i.e. they have pharmacological properties similar to those of effective antidepressants. Clozapine (71), olanzapine (71, 72) and risperidone (71, 73) have also been suggested to have antidepressive effects in patients suffering from schizophrenia. Keck and colleagues (71) have concluded that the compounds mentioned above may have therapeutic effects on depression and that clozapine and olanzapine may reduce suicide risk in these patients.

*Non-treatment related depressive symptoms.* It is well known that non-psychotic patients with substance abuse, e.g. cannabis (74) or alcohol (75), frequently develop depressive symptoms. A high proportion of patients with schizophrenia abuse alcohol (76, 77) as well as nicotine (32) and illicit drugs (78). Illicit drugs use has even increased over the last decade (33, 76). Although there is yet no direct evidence of a correlation between substance abuse and depression in patients with schizophrenia (79, 80), a correlation nevertheless seems probable. Patients with comorbid substance misuse were also more likely to report suicidal ideation (81). Alcohol abuse prior to first admission was found in 24%, drug abuse in 14% of patients with schizophrenia (82). On the other hand, Hambrecht and Häfner (82) have reported that alcohol abuse more often follows than precedes the first symptoms of schizophrenia.

Identifying drug problems remains to be a challenge for young men, especially those with a family history of substance abuse or affective disorders seem to be at higher risk. Attention to psychosocial circumstances, family history, clinical signs of withdrawal and toxicological screenings help to identify such patients.

The prevalence of undiagnosed medical diseases in chronic psychiatric out-patients ranges from 26 (83) up to 53% (84). These diseases have direct or indirect impacts on psychological health and social functioning (31, 83, 84). Examples of somatic diseases inducing depression are cancer (85) and heart failure (86). As somatic illness can cause depression it is likely that this may also occur in patients with schizophrenia. In conclusion, even if there are obvious indicators for a psychosocial etiology of depressive states in patients with schizophrenia, it is important to rule out secondary factors first. To this end, regular medical check-ups, consisting of a medical history, physical

examination and routine laboratory tests, are indicated.

### Depression *concurrent* with acute psychotic symptoms

After secondary (organic) factors for depression have been ruled out, further diagnostic steps can be taken. First, one needs to evaluate whether depression concurs with acute psychotic symptoms.

Depressive symptoms occurring as part of an acute psychotic decompensation may be difficult to attribute to a specific disorder and a reliable diagnosis can often only be made in a longitudinal view. The traditional notion that depressive symptoms in schizophrenia are limited to the post-psychotic period has been challenged, as many studies have verified that depressive symptoms are also present during the acute psychotic phase of the illness (5, 48, 87, 88). At admission, half of the acutely ill psychotic patients with schizophrenia present with significant depressive symptoms (43). While half of these patients experience a spontaneous remission of the symptoms within 3 weeks, the remaining 50% develop persistent depression (88, 89). One study even found a remission rate of 98% as the psychosis remitted (5).

A new advent of depressive symptoms in a patient with schizophrenia is certainly a serious reason for increased observation and support (50). Many patients will benefit from psychosocial programs and/or an adjustment of pharmacological treatment, although the latter may not be necessary, given the tendency of many short-lived depressive features to remit spontaneously. The addition of tricyclic antidepressants in such instances may even increase psychotic symptomatology or retard the resolution of psychosis (90); a few cases of psychotic exacerbation provoked by serotonin reuptake inhibitors (SSRIs) have also been reported (91). In patients who suffer from concomitant psychotic and depressive symptoms, schizoaffective disorder and psychotic depression have to be differentiated from schizophrenia. This important differential diagnosis is highlighted in the following paragraphs.

*Schizoaffective disorder.* Since the introduction of the term in 1933 (92), schizoaffective disorder remains one of the most controversial nosological concepts in psychiatry (93). Some groups (23, 94–98) have generally found a better outcome for patients with schizoaffective psychosis compared with patients with schizophrenia. Outcome was worse, however, when compared with patients

suffering from affective disorders. Schizoaffective disorder as a nosological entity was subsequently operationalized and became part of the Research Diagnostic Criteria (RDC) (99), DSM III R and DSM IV (100). In the absence of empirical data, an arbitrary criterion was developed. Schizoaffective disorder is to be diagnosed as an uninterrupted period of illness during which, at some time, there are affective symptoms (either a major depressive, a manic, or mixed episode) concurrent with symptoms that meet criteria (criterion A) for schizophrenia (100). In addition, criteria for an affective episode must be present for a substantial portion and delusions or hallucinations have to be identified for at least 2 weeks in absence of mood symptoms during the same episode. Schizophrenia is to be diagnosed if mood syndromes are not present for a substantial part of the psychotic illness. Depressive symptoms during the acute psychotic phase do not qualify as schizoaffective because they are mostly of brief duration. In schizoaffective disorder, psychotic symptoms must be present for at least 2 weeks without affective symptoms. The question whether schizoaffective disorder is part of the schizophrenia or affective disorders spectrum, or whether it is a disorder in its own right, remains to be clarified.

*Psychotic depression.* In DSM IV (100), psychotic depression is defined as a major depressive episode, not because of a medical condition or induced by a substance, that is accompanied by delusions or hallucinations. DSM specifies that the associated psychotic features may be mood congruent or incongruent.

Although many patients present with clear-cut concomitant depressive and psychotic features, some indeed present primarily with depressive symptoms and others primarily with psychotic features. Some depressed patients may fail to verbalize the psychotic symptoms because of severe psychomotor retardation or catatonia (101). By contrast, in patients with obvious psychosis, mood symptoms may be subtle or the patient may be unable to articulate them as a result of formal thought disorder. These patients may, therefore, not meet full DSM-IV criteria for a major depressive episode and may be misdiagnosed as schizophrenia (102). Patients with psychotic depression have been reported to remit more easily than patients with schizophrenia (103). Whether psychotic depression is a nosological entity independent from non-psychotic depression is still a matter of discussion (103–106). In schizoaffective disorder, delusions and/or hallucinations must be present without affective features

for at least 2 weeks. This arbitrary definition allows a differential diagnosis to psychotic depression, where both types of symptoms have to be present concomitantly. In addition, psychotic depression has been shown to have a better short-term outcome than schizoaffective disorder, depressed type (107). The long-term outcome of schizoaffective disorder, depressed type, resembles the outcome of patients with schizophrenia (103, 105).

If depressive symptoms are present during the acute, psychotic stage of schizophrenia, they usually respond to antipsychotic monotherapy (108). This may also aid the differential diagnosis from major depression with psychotic features, which is best treated with a combination of antidepressant/antipsychotic medication or electroconvulsive therapy (108).

Depression occurring during periods *without* acute psychotic symptoms

*Depression as a prodromal symptom.* Depressive symptoms commonly appear in the prepsychotic period, as prodromal symptoms to a first episode of schizophrenia. Häfner and colleagues (109) have developed a semistructured interview (IRAOS, Interview for the Retrospective Assessment of the Onset of Schizophrenia) to account for early symptoms of schizophrenia retrospectively. Using this instrument (110, 111), they showed that 81% of all patients ( $n = 203$ ) had developed depressive symptoms at sometime during the early course of the disease. The first depressive symptoms occurred on average 4.3 years before their first hospital admission. Forty-two per cent of these patients experienced depressive symptoms in the prepsychotic period; 18% developed psychotic and depressive symptoms concurrently, and 21% experienced depression after the first psychotic symptoms.

Others have stressed the importance of depressive features in the context of psychotic relapses. Johnson (2) has reported that depression developing after an interval of 1 year after recovery from acute symptoms indicates a significant risk of relapse within the next 2 years. Herz et al. (112) have found that depressive symptoms are frequently noticed by patients and their families just before rehospitalization. Similarly, in a 2-year prospective study, Mandel et al. (18) have documented that a relapse occurs in 64% of patients with schizophrenia who develop depression compared with 19% of those who show no depressive features. Koreen et al. (5), on the other hand, who have studied a first episode



sample, have found that only 7% of relapses were preceded by depressive symptoms.

If a patient experiences depressive symptoms during the non-psychotic stage of the illness, the clinician should also take potential psychosocial stressors into account. Close monitoring over a few weeks will reveal whether the patient is experiencing transitory depressive symptoms, an incipient psychotic decompensation, or a more chronic depressive syndrome.

*Post-psychotic depression.* Post-psychotic depression formerly depicted an often short-lived dysphoric state immediately following a psychotic episode. Since the appearance of DSM IV post-psychotic depression englobes all depressive states, occurring at any time after a psychotic episode. This definition encompasses acute dysphoric states related to stress or disappointment as well as more chronic depressive states sometimes referred to, as chronic demoralization.

The ICD 10 definition of post-psychotic depression (113) requires, along with a history of schizophrenia in the last 12 months, that the patient still exerts symptoms like hallucinations, thought disorder or negative symptoms not because of depression or medication. This definition partially overlaps with the definition of schizoaffective disorder.

*Transient depressive reactions.* Siris et al. (89) have described post-psychotic depression to be a transient phenomenon appearing in almost half of their patients with schizophrenia. In a 12-month survey of 105 patients with schizophrenia, 36% developed post-psychotic depression without a concomitant increase of psychotic symptoms (47). A majority of patients were reported to remit within 3 weeks in an early study by Schwartz and Myers (114). Such states are commonly related to psychosocial stress. This is likely one of the reasons why psychosocial therapy, if combined with antipsychotics, reduces relapse rates considerably (115). Nevertheless, as discussed above, when depressive symptoms appear in the non-psychotic patient with schizophrenia the clinician should think of an impending relapse. In addition to marked dysphoria, anxiety and somatic symptoms such as sleeplessness, are frequently seen in this context.

*Chronic demoralization.* The depressive syndrome referred to as chronic demoralization often develops more gradually (116). It may be linked to the patients' increasing of their devastating and disabling disease. Especially, patients with a feeling of

loss of control over their illness are at risk (117). Frank (118) and Klein (119) have coined the term of demoralization to refer to this severe state of impairment which can persist for years. This clinical concept, which has important prognostic consequences, found confirmation for primary care by other authors (119–122). Chronic demoralization should be considered when patients present with a chronic and persistent state of deep hopelessness and existential distress in the absence of somatic features of depression. It has been associated with a significant suicide risk. Adjunctive psychotherapy, e.g. psychoeducational family therapy or cognitive behavioral therapy is the mainstay of helping patients to cope with demoralization syndromes (123, 124).

*Differential diagnosis to the negative syndrome complex.* The differential diagnosis of depression during the course of schizophrenia is further complicated by the fact that some symptoms of schizophrenia overlap with depressive symptoms. Sleep disturbances, lack of appetite, concentration difficulties, attentional deficits and anhedonia are found in both groups (125, 126). Clinical features of both syndromes also include poverty of thought and speech, blunted affect, decreased motor activity, apathy and avolition as well as social withdrawal. Blue mood and depressed cognition were shown not to be related to the negative syndrome (127) so that clear distinctions can be made in the presence of these symptoms (128–130). Somatic symptoms, such as early morning awakening, loss of appetite and sleep disturbances may also be helpful in establishing the diagnosis of depression. Despite this, the differentiation between depression and certain components of the negative syndrome remains a clinical challenge.

*Treatment of chronic depressive states.* If depression persists in a patient being treated with a traditional antipsychotic, treatment should first consist in adding an antidepressant to the current antipsychotic medication (108, 131–133). Alternatively, clinicians may choose to switch to one of the second-generation antipsychotics. It would appear that the first strategy is easier to implement in the usual clinical setting, but the evidence clearly supports both interventions, so that the sequence of these approaches can follow clinical demands and preferences. As the phenomenology of relapse within a patient tends to be similar (110), depressive symptoms of the illness might be considered an indication for second-generation antipsychotics,

which appear to have superior antidepressant efficacy compared with traditional neuroleptics (134).

If depression persists in patients already being treated with novel antipsychotics, an adjunctive therapy with tricyclics is an evidence-based treatment option. SSRIs have also been suggested to be efficacious in this context (135–138). In consideration of the potential toxic effect of an overdose with tricyclics, SSRIs should be considered as first-line antidepressants as patients with chronic depressive features present with a high suicide risk (122, 139). The combination of some SSRIs with clozapine requires particular caution as pharmacological interactions can lead to toxic clozapine plasma concentrations (140). With the regard to mood stabilizers, additional research is needed (141).

As lithium is a medication for which the evidence consistently shows an antisuicidal effect in patients with bipolar disorder, an augmentation therapy with lithium might be considered (142) although the evidence in patients with schizophrenia is sparse (143, 144).

A switch from a classical to a second-generation compound, especially to clozapine, seems to be indicated in such instances. Meltzer has stated that clozapine appreciably reduces the risk of suicide (145, 146). In addition, many patients will benefit from a psychosocial support program (147).

Rating scales used to assess depressive symptoms in schizophrenia

Newcomer et al. (148) used existing tools, namely the Brief Psychiatric Rating Scale (BPRS) depression factor and the Hamilton Rating Scale for Depression (HAM-D) and concluded that depressive symptoms as well as positive and negative items can be reliably measured and separated with these instruments.

In 1990, Addington et al. (149) presented a new tool, the CDS for schizophrenia based on items selected from the HAM-D and the Present State Examination. In subsequent papers, the authors demonstrated the specificity of the scale in comparison with the HAM-D (150) as well as its specificity in terms of separating between depression, negative symptoms and EPS (151). Collins et al. (152) compared the HAM-D scale and the PANSS-D scale (Depression subscale of the Positive and Negative Syndrome Scale) to the CDS. Results revealed that although all three measures of depression were significantly correlated, the CDS was the most suitable measure of depression in schizophrenia.

## Conclusion

Prevalence studies of depressive symptoms in schizophrenia range from a low of 7 up to 80%. The advent of depressive symptoms in a patient with schizophrenia calls for additional diagnostic and therapeutic considerations. It is important to relate a patient's symptoms to the course of the illness. Differentiating depressive states in schizophrenia has consequences in terms of choosing therapeutic strategies. Clinicians must rule out a secondary or 'organic' etiology of depression first. Many patients will benefit from a psychosocial support program and/or a change or adjustment of pharmacological treatment, although the latter may not be necessary, given the tendency of many short-lived depressive features to remit spontaneously. Chronic depressive states should be treated by adding antidepressants to antipsychotic medication or by switching to a second-generation antipsychotic.

## References

1. HIRSCH SR, JOLLEY AG. Dysphoric syndrome in schizophrenia and its implications for relapse. *Br J Psychiatry* 1989;**155**:46–50.
2. JOHNSON DAW. The significance of depression in the prediction of relapse in chronic schizophrenia. *Br J Psychiatry* 1988;**152**:320–323.
3. ELK R, DICKMAN BJ, TEGGIN AF. Depression in schizophrenia: a study of prevalence and treatment. *Br J Psychiatry* 1986;**149**:228–229.
4. WASSINK TH, FLAUM M, NOPOULOS P, ANDREASEN NC. Prevalence of depressive symptoms in the early course of schizophrenia. *Am J Psychiatry* 1999;**156**:315–316.
5. KOREEN AR, SIRIS SG, CHOKOS M, ALVIR J, MAYERHOFF D, LIEBERMAN J. Depression in first-episode schizophrenia. *Am J Psychiatry* 1993;**150**:1643–1648.
6. LANCON C, AUQUIER P, REINE G, BERNARD D, ADDINGTON D. Relationships between depression and psychotic symptoms of schizophrenia during an acute episode and stable period. *Schizophr Res* 2001;**47**:135–140.
7. MARTIN RL, CLONINGER RC, GUZE SB, CLAYTON PJ. Frequency and differential diagnosis of depressive syndromes in schizophrenia. *J Clin Psychiatry* 1985;**46**:9–13.
8. JOHNSON DAW. Depressions in schizophrenia: some observations on prevalence, etiology, and treatment. *Acta Psychiatr Scand* 1981;**63**:137–144.
9. FENTON WS. Depression, suicide and suicide prevention in schizophrenia. *Suicide Life Threat Behav* 2000;**30**:34–49.
10. KESSLER RC, MCGONAGLE KA, ZHAO S et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994;**51**:8–19.
11. CRANCO R. Overview of affective disorders. In: KAPLAN HI, SADDOK BJ, eds. *Comprehensive textbook of psychiatry IV*. Baltimore: Williams & Wilkins, 1985.
12. BLEULER E. Die Prognose der Dementia Praecox Schizophreniegruppe. *Allgemeine Z Psychiatrie* 1908;**65**: 436–464.

## Differential diagnosis of depressed mood in patients with schizophrenia

13. KRAEPELIN E. *Psychiatrie 1896* 5th edn Leipzig. Reprint. In: CUTTING J, SHEPHERD M, eds. *The clinical roots of psychiatry*, London: Cambridge University Press, 1987.
14. VAILLANT G. Prospective prediction of schizophrenic remission. *Arch Gen Psychiatry* 1964;**11**:509–518.
15. HOEDEMAEKER FS. Postpsychotic episodes and postpsychotic depression in young adults. *Am J Psychiatry* 1970;**127**:606–610.
16. TAYLOR M, ABRAMS R. Manic-depressive illness and good-prognosis schizophrenia. *Am J Psychiatry* 1975;**132**:741–745.
17. EMSLEY RA, OOSTHUIZEN PP, JOUBERT AF, ROBERTS MC, STEIN DJ. Depressive and anxiety symptoms in patients with schizophrenia and schizophreniform disorder. *J Clin Psychiatry* 1999;**60**:747–751.
18. MANDEL MR, SEVERE JB, SCHOOLER NR. Development and prediction of postpsychotic depression in neuroleptic treated schizophrenics. *Arch Gen Psychiatry* 1982;**39**:197–203.
19. SANDS J, HARROW M. Depression during the longitudinal course of schizophrenia. *Schizophr Bull* 1999;**25**:157–171.
20. FALLOON I, WATT DC, SHEPHERD MA. A comparative controlled trial of pimozide and fluphenazine decanoate in the continuation therapy of schizophrenia. *Psychol Med* 1978;**8**:59–70.
21. JOHNSON DAW. Depression in schizophrenia: some observations on prevalence, etiology, and treatment. *Acta Psychiatr Scand* 1981;**63**:137–144.
22. ADDINGTON D, ADDINGTON J. Attempted suicide and depression in schizophrenia. *Acta Psychiatr Scand* 1992;**85**:288–291.
23. HIMMELHOCH JM, FUCHS CZ, MAY SJ, SYMONS BJ, NEIL JF. When a schizoaffective diagnosis has meaning. *J Nerv Ment Dis* 1981;**169**:277–282.
24. KOHLER C, GUR RC, SWANSON CL, PETTY R, GUR RE. Depression in schizophrenia. I. Association with neuropsychological deficits. *Biol Psychiatry* 1998;**43**:165–172.
25. HOLTHAUSEN EA, WIERSMA D, KNEGTERING RH, VAN DEN BOSCH RJ. Psychopathology and cognition in schizophrenia spectrum disorders: the role of depressive symptoms. *Schizophr Res* 1999;**39**:65–71.
26. GLAZER W, PRUSOFF B, JOHN K. Depression and social adjustment among chronic schizophrenic outpatients. *J Nerv Ment Dis* 1981;**169**:712–717.
27. CASPARI D. Cannabis and schizophrenia: results of a follow up study. *Eur Arch Psychiatry Clin Neurosci* 1999;**249**:45–49.
28. HÄFNER H, LÖFFLER W, MAURER K, HAMBRECHT MAN, DER HEIDEN W. Depression, negative symptoms, social stagnation and social decline in the early course of schizophrenia. *Acta Psychiatr Scand* 1999;**100**:105–118.
29. HÄFNER HAN, DER HEIDEN W. The course of schizophrenia in the light of modern follow-up studies: the ABC and WHO studies. *Eur Arch Psychiatry Clin Neurosci* 1999;**249**:14–26.
30. JIN H, ZISOOK S, PALMER BW, PATTERSON TL, HEATON RK, JESTE DV. Association of depressive symptoms in schizophrenia: a study in older outpatients. *J Clin Psychiatry* 2001;**62**:797–803.
31. GOLDMAN LS. Medical illness in patients with schizophrenia. *J Clin Psychiatry* 1999;**60**:10–15.
32. KELLY C, MCCREADIE RG. Smoking habits, current symptoms, and premorbid characteristics of schizophrenic patients in Nithsdale, Scotland. *Am J Psychiatry* 1999;**156**:1751–1757.
33. PATKAR AA, ALEXANDER RC, LUNDY A, CERTA KM. Changing patterns of illicit substance abuse among schizophrenic patients: 1984–1996. *Am J Addict* 1999;**8**:65–71.
34. ADDINGTON D, ADDINGTON J, ROBINSON G. Attributional style and depression in schizophrenia. *Can J Psychiatry* 1999;**44**:697–700.
35. ROY A. Suicide in chronic schizophrenia. *Br J Psychiatry* 1982;**141**:171–177.
36. DRAKE RE, GATES C, WHITAKER A, COTTON PG. Suicide among schizophrenics. *Compr Psychiatry* 1985;**26**:90–100.
37. BLACK DW, WINOKUR G, WARRACK G. Suicide in schizophrenia: the Iowa record linkage study. *J Clin Psychiatry* 1985;**46**:14–17.
38. SHAH A, GANESVARAN T. Suicide among psychiatric in-patients with schizophrenia in an Australian mental hospital. *Med Sci Law* 1999;**39**:251–259.
39. BOTTLENDER R, STRAUSS A, MÖLLER HJ. Prevalence and background factors of depression in first admitted schizophrenic patients. *Acta Psychiatr Scand* 2000;**101**:153–160.
40. GUPTA S, BLACK DW, ARNDT S, HUBBARD WC, ANDREASEN NC. Factors associated with suicide attempts among patients with schizophrenia. *Psychiatr Serv* 1998;**49**:1353–1355.
41. HARKAVY-FRIEDMAN JM, RESTIFO K, MALASPINA D et al. Suicidal behavior in schizophrenia: characteristics of individuals who had and had not attempted suicide. *Am J Psychiatry* 1999;**156**:1276–1278.
42. KNIGHTS A, HIRSCH SR. Revealed depression and drug treatment for schizophrenia. *Arch Gen Psychiatry* 1981;**38**:806–811.
43. MÖLLER HJ, VON ZERSSEN D. Depressive states occurring during the neuroleptic treatment of schizophrenia. *Schizophr Bull* 1982;**8**:109–117.
44. BAYNES D, MULHOLLAND C, COOPER SJ et al. Depressive symptoms in stable chronic schizophrenia: prevalence and relationship to psychopathology and treatment. *Schizophr Res* 2000;**45**:47–56.
45. NAKAYA M, OHMORI K, KOMAHASHI T, SUWA H. Depressive symptoms in acute schizophrenic inpatients. *Schizophrenia Res* 1997;**25**:131–139.
46. ZISOOK S, McADAMS LA, KUCK J et al. Depressive symptoms in schizophrenia. *Am J Psychiatry* 1999;**156**:1736–1743.
47. BIRCHWOOD M, IQBAL Z, CHADWICK P, TROWER P. Cognitive approach to depression and suicidal thinking in psychosis. I. Ontogeny of postpsychotic depression. *Br J Psychiatry* 2000;**177**:516–521.
48. MCGLASHAN TH, CARPENTER WT. Postpsychotic depression in schizophrenia. *Arch Gen Psychiatry* 1976;**33**:231–239.
49. HEINRICH K. Zur Bedeutung des postremissiven Erschöpfungssyndroms für die Rehabilitation Schizophrener. *Nervenarzt* 1967;**38**:487–491.
50. SIRIS SG. Depression in schizophrenia. perspective in the era of ‘atypical’ antipsychotic agents. *Am J Psychiatry* 2000;**157**:1379–1389.
51. SUBOTNIK KL, NUECHTERLEIN KH, ASARNOW RF, FOLGESON DL, GOLDSTEIN MJ, TALOVIC SA. Depressive symptoms in the early course of schizophrenia: relationship to familial psychiatric illness. *Am J Psychiatry* 1997;**154**:1551–1556.
52. BLACKWOOD DH, FORDYCE A, WALKER MT, STCLAIR DM, PORTEUS DJ, MUIR WJ. Schizophrenia and affective disorders – cosegregation with a translocation at chromosome 1q42 that directly disrupts brain-expressed genes. Clinical and P300 findings in a family. *Am J Hum Genet* 2001;**69**:428–433.

53. ASHERTON P, MANT R, WILLIAMS N et al. Study of chromosome 4p markers and dopamine D5 receptor gene in schizophrenia and bipolar disorder. *Mol Psychiatry* 1998;**3**:310–320.
54. HYMAN SE. The genetics of mental illness. Implications for practice. *Bull World Health Organ* 2000;**78**:455–463.
55. ZUBIN J, SPRING B. Vulnerability. A new view of schizophrenia. *J Abnorm Psychol* 1977;**86**:103–126.
56. NUECHTERLEIN KH, DAWSON MD. A heuristic vulnerability-stress model of schizophrenic episodes. *Schiz Bull* 1984;**10**:300–312.
57. TSUANG M. Schizophrenia: genes and environment. *Biol Psychiatry* 2000;**47**:210–220.
58. SIRIS SG, ADDINGTON D, AZORIN JM, FALLOON RH, GERLACH J, HIRSCH SR. Depression in schizophrenia: recognition and management in the USA. *Schizophr Res* 2001;**47**:185–197.
59. HOGARTY GE, MUNETZ MR. Pharmacogenic depression among outpatient schizophrenic patients: a failure to substantiate. *J Clin Psychopharmacol* 1984;**4**:17–24.
60. HIRSCH SR, JOLLEY AG, BARNES TR et al. Dysphoric and depressive symptoms in chronic schizophrenia. *Schizophr Res* 1989;**2**:259–264.
61. RIFKIN A, QUITKIN F, KLEIN DF. Akinesia: a poorly recognized drug-induced extrapyramidal behavioral disorder. *Arch Gen Psychiatry* 1975;**32**:672–674.
62. VAN PUTTEN T, MAY PRA. Akinetic depression in schizophrenia. *Arch Gen Psychiatry* 1978;**35**:1101–1107.
63. MILLER CH, FLEISCHHACKER WW. Neurologische Neuroleptika-Nebenwirkungen. In: FÖRSTL H, ed. *Klinische Neuropsychiatrie*. Stuttgart, New York: Georg Thieme Verlag, 2000:449–478.
64. DRAKE RE, EHRlich J. Suicide attempts associated with akathisia. *Am J Psychiatry* 1985;**142**:499–501.
65. FLEISCHHACKER WW, BERGMANN KJ, PEROVICH R et al. The Hillside akathisia scale: a new rating instrument for neuroleptic-induced akathisia. *Psychopharmacol Bull* 1989;**25**:222–226.
66. KANBA S, YAGI G, OGUCHI E et al. Neuropharmacology of zotepine, an antimanic drug: a potent blocker of D2 and 5-HT2 receptors of human brain. *Jpn J Psychiatr Neurol* 1991;**45**:133–134.
67. ROTH BL, CRAIGO SC, CHOUDHARY MS et al. Binding of typical and atypical antipsychotic agents to 5-hydroxytryptamine-6 and 5-hydroxytryptamine-7 receptors. *J Pharmacol Exp Ther* 1994;**268**:1403–1410.
68. ROWLEY HL, KILPATRICK IC, NEEDHAM PL et al. Elevation of extracellular cortical noradrenaline may contribute to the antidepressant activity of zotepine: an in vivo microdialysis study in freely moving rats. *Neuropharmacology* 1998;**37**:937–944.
69. SEEGER TF, SEYMOUR PA, SCHMIDT AW et al. Ziprasidone (CP-88.059): a new antipsychotic with combined dopamine and serotonin receptor antagonist activity. *J Pharmacol Exp Ther* 1995;**275**:101–113.
70. KECK PE JR, BUFFENSTEIN A, FERGUSON J et al. Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo-controlled trial. *Psychopharmacol-Berl* 1998;**140**:173–184.
71. KECK PE JR, STRAKOWSKI SM, MCELROY SL. The efficacy of atypical antipsychotics in the treatment of depressive symptoms, hostility, and suicidality in patients with schizophrenia. *J Clin Psychiatry* 2000;**61**:4–9.
72. TOLLEFSON GD, SANGER TM. Negative symptoms: a path analytic approach to a double-blind placebo and haloperidol controlled clinical trial with olanzapine. *Am J Psychiatry* 1997;**154**:466–474.
73. PEUSKENS J. Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. *Br J Psychiatry* 1995;**166**:712–726.
74. BOVASSO GB. Cannabis abuse as a risk factor for depressive symptoms. *Am J Psychiatry* 2001;**158**:2033–2037.
75. SITHARTHAN G, HOUGH MJ, SITHARTHAN T, KAVANAGH DJ. The alcohol helplessness scale and its prediction of depression among problem drinkers. *J Clin Psychol* 2001;**57**:1445–1457.
76. FOWLER IL, CARR VJ, CARTER NT, LEWIN TJ. Patterns of current and lifetime substance use in schizophrenia. *Schizophr Bull* 1998;**24**:443–455.
77. CANTWELL R, BREWIN J, GLAZEBROOK C. Prevalence of substance misuse in first-episode psychosis. *Br J Psychiatry* 1999;**174**:150–153.
78. SAFER DJ. Substance abuse by young adult chronic patients. *Hosp Community Psychiatry* 1987;**38**:511–514.
79. SCHUCKIT A. Alcoholism and other psychiatric disorders. *Hosp Community Psychiatry* 1983;**34**:1022–1027.
80. BARTELS SJ, DRAKE RE, MCHUGO GJ. Alcohol abuse, depression and suicidal behavior in schizophrenia. *Am J Psychiatry* 1992;**149**:394–395.
81. KAMALI M, KELLY L, GERVIN M, BROWNE S, LARKIN C, O'CALLAGHAN E. The prevalence of comorbid substance misuse and its influence on suicidal ideation among in-patients with schizophrenia. *Acta Psychiatr Scand* 2000;**101**:452–456.
82. HAMBRECHT M, HÄFNER H. Substance abuse and the onset of schizophrenia. *Biol Psychiatry* 1996;**40**:1155–1163.
83. BARNES RF, MASON JC, GREER C et al. Medical illness in chronic psychiatric outpatients. *Gen Hosp Psychiatry* 1983;**5**:191–195.
84. FARMER S. Medical problems of chronic patients in a community support program. *Hosp Community Psychiatry* 1987;**38**:745–749.
85. ANGELINO AF, TREISMAN GJ. Major depression and demoralization in cancer patients: diagnostic and treatment considerations. *Support Cancer* 2001;**9**:344–349.
86. ROZZINI R, SABATINI T, FRISONI GB, TRABUCCHI M. Depression and major outcomes in older patients with heart failure. *Arch Intern Med* 2002;**162**:362–364.
87. PLANANSKY K, JOHNSTON R. Depressive syndrome in schizophrenia. *Acta Psychiatr Scand* 1987;**57**:207–218.
88. STRAINE F, HEGER R, KLICKPERA C. The time structure of depressive mood in schizophrenic patients. *Acta Psychiatr Scand* 1982;**65**:66–73.
89. SIRIS SG, RIFKIN A, REARDON GT, DODDI SR, STRAHAN A, HALL KS. Stability of the postpsychotic depression syndrome. *J Clin Psychiatry* 1986;**47**:86–88.
90. KRAMER MS, VOGEL WH, DIJOHNSON C. Antidepressants in depressed schizophrenic inpatients. *Arch Gen Psychiatry* 1989;**46**:922–928.
91. SILVER H, JAHJAH N, KUSHNIR M. Psychotic symptoms in schizophrenics during chronic fluvoxamine treatment. A report of two cases. *Schizophr Res* 1995;**16**:77–79.
92. KASANIN J. The acute schizoaffective psychosis. *Am J Psychiatry* 1933;**90**:97–126.
93. POPE JR HG, LIPINSKI JF, COHEN BM, AXELRODT DT. 'Schizoaffective disorder' an invalid diagnosis? A comparison of schizoaffective disorder, schizophrenia, and affective disorder. *Am J Psychiatry* 1980;**137**:921–927.
94. WELNER A, CROUGHAN JL, ROBINS E. The group of schizoaffective and related psychosis-critique, record,

## Differential diagnosis of depressed mood in patients with schizophrenia

- follow up and family studies: a persistent enigma. *Arch Gen Psychiatry* 1974;**34**:628–631.
95. ABRAMS R, TAYLOR MA. Mania and schizoaffective disorder, manic type: a comparison. *Am J Psychiatry* 1976;**133**:1445–1447.
  96. TSUANG MT, DEMPSEY GM. Long-term outcome of major psychosis II. Schizoaffective disorder compared with schizophrenia, affective disorders and a surgical control group. *Arch Gen Psychiatry* 1979;**36**:1302–1304.
  97. ROSENTHAL NE, ROSENTHAL LN, STALLONE F, DUNNER DL, FIEVE RR. Toward the validation of RDC schizoaffective disorder. *Arch Gen Psychiatry* 1980;**37**:804–810.
  98. BROCKINGTON IF, WAINWRIGHT S, KENDELL RE. Manic patients with schizophrenic or paranoid symptoms. *Psychol Med* 1980;**10**:73–83.
  99. SPITZER RL, ENDICOTT J, ROBINS E. Research diagnostic criteria. rationale and reliability. *Arch Gen Psychiatry* 1978;**35**:773–782.
  100. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edn. Washington DC: American Psychiatric Press, 1994: 711–712.
  101. PARKER G, HADZI-PAVLOVIC D, HICKIE I et al. Psychotic depression: a review and clinical experience. *Aust NZ J Psychiatry* 1991;**25**:169–180.
  102. ROTHSCHILD AJ. Management of psychotic, treatment-resistant depression. *Psychiatr Clin North Am* 1996;**19**: 237–252.
  103. TSUANG D, CORYELL WC. An 8-year follow-up of patients with DSM-III-R psychotic depression, schizoaffective disorder and schizophrenia. *Am J Psychiatry* 1993;**150**:1182–1188.
  104. JESTE DV, HEATON SC, PAULSEN JS, ERCOLI L, HARRIS J, HEATON RK. Clinical and neuropsychological comparison of psychotic depression with nonpsychotic depression and schizophrenia. *Am J Psychiatry* 1997;**4**:490–496.
  105. MAJ M, STARACE F, PIROZZI R. A family study of DSM-III-R schizoaffective disorder, depressive type, compared with schizophrenia and psychotic and nonpsychotic major depression. *Am J Psychiatry* 1991;**5**:612–616.
  106. SCHATZBERG AF, ROTHSCHILD AJ. Psychotic (delusional) major depression: should it be included as a distinct syndrome in DSM-IV. *Am J Psychiatry* 1992;**149**:733–745.
  107. CORYELL W, KELLER M, LAVORI P et al. Affective syndromes, psychotic features and prognoses. I. Depression. *Arch Gen Psychiatry* 1990;**47**:651–657.
  108. HAUSMANN A, FLEISCHHACKER WW. Depression in patients with schizophrenia: prevalence and diagnostic and treatment considerations. *CNS-Drugs* 2000;**14**: 289–299.
  109. HÄFNER H, RIECHER-RÖSSLER A, HAMBRECHT M et al. IRAOS: an instrument for the assessment of onset and early course of schizophrenia. *Schizophr Res* 1992;**6**:209–223.
  110. BUSTAMANTE S, MAURER K, LÖFFLER W, HÄFNER H. Depression im Frühverlauf der Schizophrenie. *Fortschr Neurol Psychiatr* 1994;**62**:317–329.
  111. HÄFNER H, MAURER K, LÖFFLER W et al. The ABC schizophrenia study: a preliminary overview of the results. *Soc Psychiatry Psychiatr Epidemiol* 1998;**33**:380–386.
  112. HERZ M. Prodromal symptoms and prevention of relapse in schizophrenia. *J Clin Psychiatry* 1985;**46**:22–25.
  113. World Health Organization. The tenth revision of the international classification of diseases and related health problems (ICD-10). Geneva: WHO, 1992.
  114. SCHWARTZ CC, MYERS JK. Life events and schizophrenia I and II. *Arch Gen Psychiatry* 1977;**34**:1238–1245.
  115. HOGARTY GE, ULRICH RF. The limitations of antipsychotic medication on schizophrenia relapse and adjustment and the contributions of psychosocial treatment. *J Psychiatr Res* 1998;**32**:243–250.
  116. BARTELS SJ, DRAKE RE. Depressive symptoms in schizophrenia: comprehensive differential diagnosis. *Compr Psychiatry* 1988;**29**:467–483.
  117. BIRCHWOOD M, MASON R, MACMILLAN F, HEALY J. Depression, demoralization and control over psychotic illness: a comparison of depressed and non-depressed patients with chronic psychosis. *Psychol Med* 1993;**23**:387–395.
  118. FRANK JD. Persuasion and healing. Baltimore: John Hopkins University Press, 1973.
  119. KLEIN DF. Endomorphic depression: a conceptual and terminological revision. *Arch Gen Psychiatry* 1974;**31**:447–454.
  120. DEFIGUEIREDO JM. Depression and demoralization: phenomenologic differences and research perspectives. *Compr Psychiatry* 1993;**34**:308–311.
  121. MOORE O, CASSIDY E, CARR A, O'CALLAGHAN E. Unawareness of illness and its relationship with depression and self-deception in schizophrenia. *Eur Psychiatry* 1999;**14**:264–269.
  122. KISSANE DW, CLARKE DM, STREET AF. Demoralization syndrome—a relevant psychiatric diagnosis for palliative care. *J Palliat Care* 2001;**17**:12–21.
  123. BUSTILLO J, LAURIELLO J, HORAN W, KEITH S. The psychosociological treatment of schizophrenia: an update. *Am J Psychiatry* 2001;**2**:163–175.
  124. TURKINGTON D, KINGDON D. Cognitive-behavioural techniques for general psychiatrists in the management of patients with psychoses. *Br J Psychiatry* 2000;**177**: 101–106.
  125. CROW TJ. Molecular pathology of schizophrenia: more than one disease process? *Br Med J* 1980;**280**:66–68.
  126. ROMNEY DM, CANDIDO CL. Anhedonia in depression and schizophrenia: a reexamination. *J Nerv Ment Dis* 2001;**189**:735–740.
  127. KIBEL DA, LAFFONT I, LIDDLE PF. The composition of the negative syndrome of chronic schizophrenia. *Br J Psychiatry* 1993;**162**:744–750.
  128. BARNES TRE, CURSON DA, LIDDLE PF, PATEL M. The nature and prevalence of depression in chronic schizophrenic in-patients. *Br J Psychiatr* 1989;**154**:486–491.
  129. KUCK J, ZISOOK S, MORANVILLE JT, HEATON RK, BRAFF DL. Negative symptomatology in schizophrenic outpatients. *J Nerv Ment Dis* 1992;**180**:510–515.
  130. MULLER MJ, SZEGEDI A, WETZEL H, BENKERT O. Depressive factors and their relationships with other symptom domains in schizophrenia, schizoaffective disorder and psychotic depression. *Schizophr Bull* 2001;**27**: 19–28.
  131. SIRIS SG. Depression and schizophrenia. In: HIRSCH SR, WEINBERGER DR, eds. *Schizophrenia*. UK: Blackwell Science Ltd., 1995.
  132. SIRIS SG, VAN KAMMEN DP, DOCHERTY JP. Use of antidepressant drugs in schizophrenia. *Arch Gen Psychiatry* 1978;**35**:1368–1377.
  133. LEVINSON DF, UMAPATHY C, MUSTHAQ M. Treatment of schizoaffective disorder and schizophrenia with mood symptoms. *Am J Psychiatry* 1999;**156**:1138–1148.
  134. FLEISCHHACKER WW. Drug treatment of patients with schizophrenia. In: HENN FA, HELMCHEN H, LAUTER H, SARTORIUS N, eds. *Contemporary psychiatry*, Vol. 3. Berlin, Heidelberg, New York: Springer Verlag, 2001:139–158.

135. GOFF DC, BROTMANN AW, WALTES M, McCORMICK S. Trial of fluoxetine added to neuroleptics for treatment resistant schizophrenic patients. *Am J Psychiatry* 1990;**147**:492–494.
136. EVINS AE, GOFF DC. Adjunctive antidepressant drug therapies in the treatment of negative symptoms of schizophrenia. *Drug Ther* 1996;**6**:130–147.
137. KASKOW JW, MOHAMED S, THALLASINOS A, CARROLL B, ZISOOK S, JESTE DV. Citalopram augmentation of anti-psychotic treatment in older schizophrenia patients. *Int J Geriatr Psychiatry* 2001;**16**:1163–1167.
138. ROSENBERG PB, ROSSE RB, SCHWARTZ BL, DEUTSCH SI. Nefazodone in the adjunctive therapy of schizophrenia. An open-label exploratory study. *Clin Neuropharmacol* 2000;**23**:222–225.
139. SIRIS SG. Suicide and schizophrenia. *J Psychopharmacol* 2001;**15**:127–135.
140. CENTORRINO F, BALDESSARINI RJ, FRANKENBURG FR, KANDO J, VOLPICELLI SA, FLOOD JG. Serum levels of clozapine and norclozapine in patients treated with selective serotonin reuptake inhibitors. *Am J Psychiatry* 1996;**153**:820–822.
141. ESCAMILLA MA. Diagnosis and treatment of mood disorders that co-occur with schizophrenia. *Psychiatr Serv* 2001;**52**:911–919.
142. TONDO L, GHIANI C, ALBERT M. Pharmacological interventions in suicide prevention. *J Clin Psychiatry* 2001;**62**:51–55.
143. LERNER Y, MINTZER Y, SCHESTATZKY M. Lithium combined with haloperidol in schizophrenic patients. *Br J Psychiatry* 1988;**153**:359–362.
144. COLLINS PJ, LARKIN EP, SHUBSACHS AP. Lithium carbonate in chronic schizophrenia – a brief trial of lithium carbonate added to neuroleptics for treatment of resistant schizophrenic patients. *Acta Psychiatr Scand* 1991;**84**:150–154.
145. MELTZER HY. Clozapine and suicide. *Am J Psychiatry* 2002;**159**:323–324.
146. MELTZER HY. Treatment of suicidality in schizophrenia. *Ann N Y Acad Sci* 2001;**932**:44–58.
147. FENTON WS, SCHOOLER NR. Evidence-based psychosocial treatment for schizophrenia. *Schizophr Bull* 2000;**26**:1–3.
148. NEWCOMER JW, FAUSTMAN WO, YEH W, CSERNANSKY JG. Distinguishing depression and negative symptoms in unmedicated patients with schizophrenia. *Psychiatry Res* 1990;**31**:243–250.
149. ADDINGTON D, ADDINGTON J, SCHISSEL B. A depression rating scale for schizophrenics. *Schizophr Res* 1990;**3**:247–251.
150. ADDINGTON D, ADDINGTON J, ATKINSON M. A psychometric comparison of the Calgary Depression Scale for Schizophrenia and the Hamilton Depression Rating Scale. *Schizophr Res* 1996;**19**:205–212.
151. ADDINGTON D, ADDINGTON J, MATICKA-TYNDAL E. Specificity of the Calgary Scale for schizophrenics. *Schizophr Res* 1994;**11**:239–244.
152. COLLINS AA, REMINGTON G, COULTER K, BIRKETT K. Depression in schizophrenia: a comparison of three measures. *Schizophr Res* 1996;**20**:205–209.