

## 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

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-

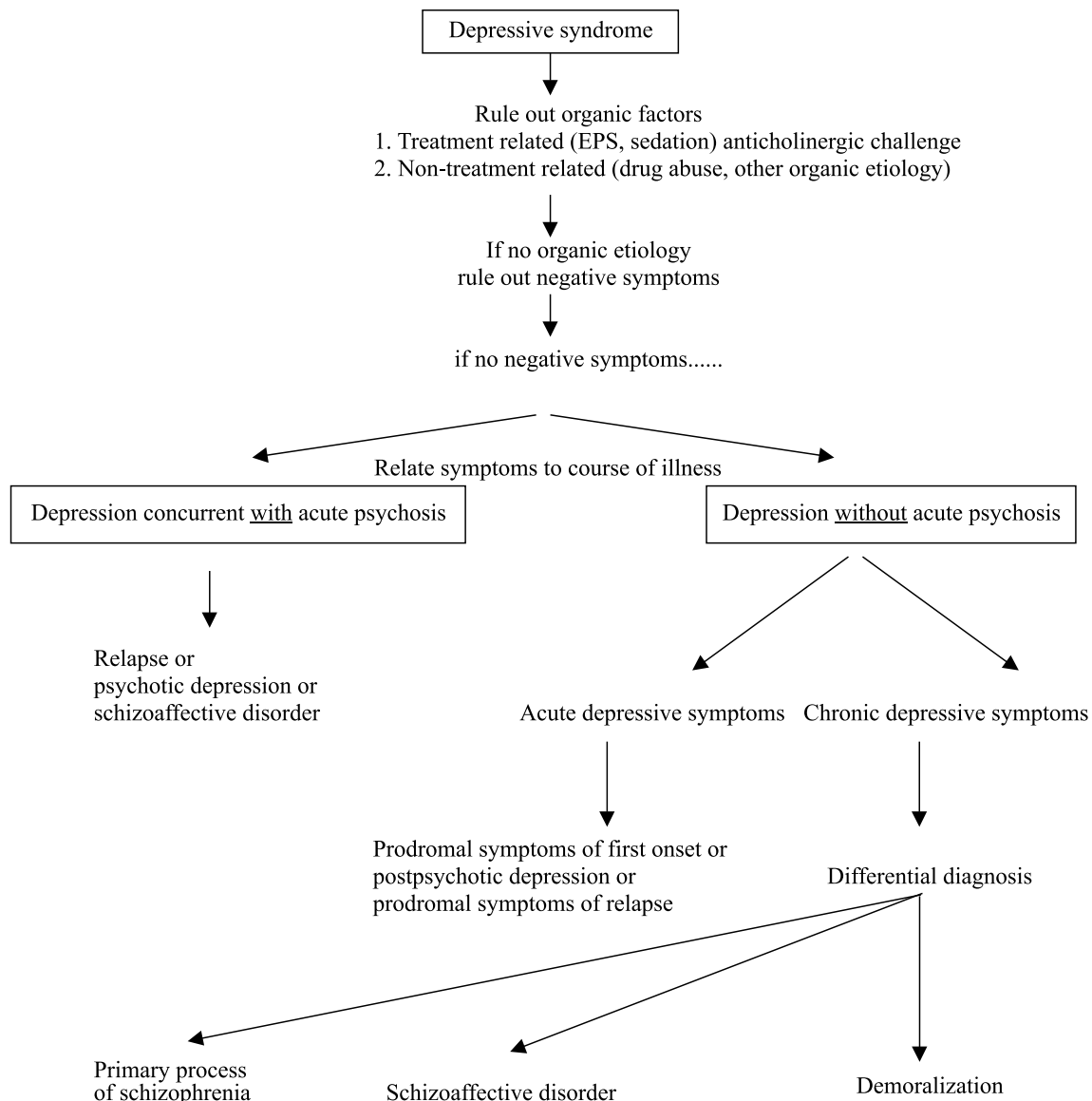


Fig. 1. Diagnostic algorithm of depressive syndromes in schizophrenia.

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 MRC	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	27 37 62	Schizophrenia	PSE	Depressive symptoms in acute schizophrenia decrease after effective neuroleptic treatment
Johnson (1981) (8)	Longitudinal assessment of depressive symptoms over a period of 8 years	37	Schizophrenia	BDI BPRS	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	EPRS IMPS	Neuroleptics are unlikely to be the major cause for depression
Hogarty and Munez (1984) (59)	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 BDI	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	ESQ SCL-90	Significantly more patients in the placebo group experienced dysphoric episodes compared with the fluphenazine group
Barnes et al. (1989) (127)	Cross-sectional study of clinical characteristics in chronic in-patients	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)	Double blind study comparing haloperidol/tricyclics to haloperidol/placebo	58	Schizophrenia schizoaffective disorder	BPRS HDRS	Adjunctive antidepressants are not indicated for the treatment of depression in actively psychotic in-patients
Newcomer et al. (1990) (147)	Cross-sectional analysis of depression and negative symptoms in unmedicated patients	69	Schizophrenia	HRSD BPRS	Negative and depressive symptoms can be assessed independently
Addington and Addington (1992) (22)	Cross-sectional assessment of depression and suicidal thinking at two time points	50	Schizophrenia	NA	Suicide attempts significantly correlated with depression on admission and after 6 months

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 EPDS 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	<i>n</i>	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 AMDIP	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); ESD: 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 (HAMD) 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 HAMD and the Present State Examination. In subsequent papers, the authors demonstrated the specificity of the scale in comparison with the HAMD (150) as well as its specificity in terms of separating between depression, negative symptoms and EPS (151). Collins et al. (152) compared the HAMD 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.

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