

Current Issues in the Classification of Psychotic Major Depression

Jennifer Keller^{1,2}, Alan F. Schatzberg², and Mario Maj³

²Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Road, Stanford, CA 94305-5723; ³Department of Psychiatry, University of Naples SUN, Naples, Italy

Depression is one of the most common mental disorders worldwide. There are a number of depression subtypes, and there has been much debate about how to most accurately capture and organize the features and subtypes of major depression. We review the current state of categorizing unipolar major depression with psychotic features (psychotic major depression, PMD), including clinical, biological, and treatment aspects of the disorder. We then propose some improvements to the current unipolar major depression categorization system. Finally, we identify important issues in need of further research to help elucidate the subtype of unipolar PMD.

Key words: major depression/psychosis/classification

Depression is one of the most common mental disorders worldwide, with a current prevalence estimated between 2.1% and 7.6%.^{1–4} A number of depressive subtypes have been identified, and there has been much debate about how to most accurately describe them. The current state of designating major depression with psychotic features (psychotic major depression, PMD) under the severity dimension is less than optimal leading to 2 pressing issues. First, should PMD be classified as a separate subtype of major depression? Second, what should or could be done to improve the current severity dimension classification?

The prevalence of psychotic depression suggests that it is worth examining a reclassification. A recent study^{5,6} reported that in the general population in 5 European countries, 2.4% of those surveyed met criteria for unipolar major depression, of whom, nearly 19% also had psychotic features. Thus, this study reported a prevalence of 0.4% of major depression with psychotic features. The percentage of major depressives with psychotic features is consistent with estimates of 15% of major depressives reporting a lifetime history of psychosis in the United States.⁷

There has been significant progress made in the last 10 years in our knowledge and understanding of PMD. There are considerable data to suggest that PMD and nonpsychotic major depression (NPMD) are separate syndromes, with different biological features, treatment response, and clinical course.^{8,9} However, there are those who argue that the data are not uniformly consistent and that the discriminators may not be sensitive or specific enough to warrant a totally separate designation. A complete discussion of this debate is beyond the scope of this article, and the readers are referred to the last major review on this topic.⁹ Even if one does not designate the disorder as a separate syndrome, the current severity dimension classification schemata have many problems and needs to be revised. In this article, we first update the status of key potential characteristics and then discuss new dimensional solutions to classifying major depression.

Clinical Symptoms

Research suggests that specific symptoms appear to be more severe in PMD patients. For example, Rothschild et al¹⁰ reported that, while PMD patients had higher depression scores than NPMD, this was primarily due to elevations on the retardation and cognitive disturbance items in PMD patients. Researchers have consistently reported more frequent and severe psychomotor difficulties (either agitation or retardation)^{11,12} and increased feelings of guilt^{12–14} in PMD.

In a recent article, Keller et al¹⁵ reported that PMD and NPMD patients, roughly matched for endogenous symptoms, were readily distinguished by ratings of the Positive Symptom subscale (PSS) on the Brief Psychiatric Rating Scale¹⁶ (BPRS), particularly the Unusual Thought Content (UTC) item. Very mild UTC endorsement, which indicates symptoms that fall short of being fully delusional, was an indicator of PMD. Moreover, the results suggested that any elevation, even very mild, on the PSS of the BPRS (ie, conceptual disorganization, suspiciousness, hallucinations, and UTC) was even better at differentiating PMD from NPMD patients. Sensitivity and specificity for this scale were 84% and 99%, respectively. Beyond delusions and hallucinations, Parker and colleagues¹⁴ found that PMDs were distinct from NPMD melancholic patients on psychomotor disturbance, depressive content, diurnal variation, and constipation.

¹To whom correspondence should be addressed; tel: 650-724-0070, fax: 650-723-8331, e-mail: jkeller@stanford.edu.

Even when researchers have matched patients for total depression scores, PMD patients demonstrated higher scores on psychomotor disturbances.¹³

A number of other symptoms have been reported to be greater in PMDs as compared with NPMDs, including depressed mood, paranoia, hypochondriasis, and anxiety. However, the empirical support for these is less robust and less consistent than are data supporting higher levels of UTC, psychomotor disturbances, and increased guilt. Thus, it appears that, although PMDs often have higher depression scores, this is likely due to specific, rather than a global, symptom elevation.

Clinical Course

The course of the depressive episodes has been found to be different in those who also exhibit psychotic features. Indeed, PMD patients often have longer duration of episodes^{17,18} and a greater likelihood of recurrence of depression.^{12,19} Moreover, patients with an index episode of psychotic depression tend to have previous episodes with psychosis.^{9,11,20} Most of the studies, however, have been retrospective. In a recent prospective study, Maj and colleagues¹⁸ found that the time to syndromal recovery from index episode was longer for PMDs than for nonpsychotic depressed patients.

There is some suggestion that PMDs have a higher morbidity as well as a higher suicide rate, although the latter is controversial.^{21,22} In their 10-year follow-up study of 452 patients with an index episode of major depression, Maj *et al*¹⁸ found that the presence of delusions (but not of sustained preoccupations) in that episode was associated with a higher depressive morbidity during the prospective observation period, but not with a worse psychopathological and psychosocial outcome at the 10-year follow-up interview. This may indicate that the prognostic significance of delusions in major depression tends to become weaker over the long term, in line with the observation by Coryell and Tsuang.²³ Vythilingam *et al*²² also found that psychotic depression was associated with a 2-fold increase in mortality compared with depression without psychotic features. These findings held true after controlling for age and additional medical illness and were not due to elevated suicide rates. Overall, patients with psychotic depression tend to have longer duration of episodes, greater recurrence, and greater morbidity than those with nonpsychotic depression.

Familial History

Relatively little is known about familial history of unipolar major depression with psychotic features. Although we know that other specific psychiatric illnesses such as bipolar disorder and schizophrenia tend to be familial,^{24,25} there are limited data on psychotic depression. A few early studies have reported that patients with

PMD had an increased risk of family prevalence of unipolar major depression^{26,27} and bipolar I disorder.²⁶ Others have found that family history of unipolar depression was similar between PMD and NPMD patients.²³

A relationship between PMD and bipolar disorder has been repeatedly suggested on the basis of family history.²⁸ In their recent prospective follow-up study of 452 patients with an index episode of major depression, Maj *et al*¹⁸ found that patients with delusions in their index episode were significantly more likely to have a family history of bipolar I disorder than those without either delusions or sustained preoccupations. Moreover, 10.1% of patients with delusions in their index episode had a manic or hypomanic episode during the 10-year follow-up, compared with 3.2% of patients who had sustained preoccupations but not delusions in their index episode, and 5.0% of those without either delusions or sustained preoccupations. The switch to bipolarity was significantly associated with an earlier first psychiatric contact and a family history of bipolar I disorder but not with the presence of delusions in the index episode. Early-onset psychotic depression has been associated with a likely bipolar course in other studies.^{29,30} More systematic gathering of family data for unipolar major depression is required before firm conclusions can be drawn regarding the familiarity of major depression with psychotic features.

Cognitive Symptoms

Recently, research has found that PMDs, as compared with NPMDs and healthy controls, have greater deficits in various tests of cognition.³¹ The most consistently replicated findings have been deficits in executive functioning,^{31–36} verbal declarative memory,^{31–33,37} and attention.^{32,33,38} In addition, some studies have found deficits in response inhibition,³¹ verbal story learning,³⁵ and visual-spatial perception and memory.^{32,34}

As discussed in Gomez *et al*,³³ there does not appear to be a generalized deficit in PMDs, but they perform worse than NPMDs and healthy controls on specific tasks. Importantly, PMDs have been found to have intact simple attention, which suggests that PMDs' ability to attend passively to units of information is within normal limits. However, they have more difficulty in processing, manipulating, and encoding new information. Furthermore, in a recent review and meta-analysis that included 5 available neuropsychological studies of PMDs,³⁹ the greatest cognitive deficits of PMDs compared with NPMDs were observed in verbal memory, executive functioning, and psychomotor speed. An issue that remains with this work is the medication status of the PMD patients because these patients are likely to have been exposed to, if they were not currently taking, antipsychotic medications, and it is unclear what effect this may have on cognition.

An earlier study by our group reported similar deficits in unmedicated PMDs compared with NPMDs and controls.³¹ A recent study attempted to circumvent this medication problem and examined first-episode PMD, schizoaffective disorder, and schizophrenia patients, none of whom had been exposed to antipsychotic medication, and compared them with nonpsychotic unipolar depression (not first episode) and healthy controls.³⁴ They reported neuropsychological differences between the groups, including between the psychotic and nonpsychotic depressed patients. The authors concluded that “the data not only provide additional support for psychotic depression as a distinct mood disorder (from nonpsychotic depression) but also document the considerable neuropsychological morbidity associated with the disorder.” They further found significant similarities between the neuropsychological profiles of the schizophrenic and psychotic depressed groups, suggesting that similar brain systems may be affected in both these disorders. Thus, there appears to be ample evidence for distinct neuropsychological profiles between PMD and NPMD, although limited research suggests that PMDs may be more similar to but slightly less severe than those with other psychotic disorders.

Biological Features

Patients with PMD have highly replicable findings of greater hypothalamic pituitary adrenal axis (HPA) activation: high rates of nonsuppression on the dexamethasone suppression test (DST), elevated post-dexamethasone cortisol levels, and high levels of 24-h urinary free cortisol.^{40–43} These findings are not just due to difference in the severity of the depression.^{44,45} In addition, Anton⁴⁰ found that it was the older PMD patients who had the highest cortisol levels, suggesting an interaction between age and type of depression. We recently found that those depressed patients with psychotic features had higher evening baseline cortisol levels.⁴⁶ Furthermore, Rothschild et al⁴² compared 4 PM post-dexamethasone cortisol levels in PMD patients to those with schizophrenia and healthy controls. They found higher afternoon cortisol levels in PMD patients but not in those with schizophrenia. They concluded that the high cortisol levels were not due to psychosis per se, but rather to the presence of psychosis in the context of an affective disorder. Hence, there appears to be even greater HPA axis activity in PMD than in NPMD.

In pooled analyses, psychotic major depressives appear to have higher rates of nonsuppression on the DST and very elevated post-dexamethasone cortisol levels⁴¹; DST nonsuppression rates in PMD are about 64%, significantly higher than the 41% seen in NPMD. The sensitivity and specificity of the DST in PMD, however, are not high enough to be used routinely for diagnosis. Some studies, albeit generally small in size, even failed to

show differences in nonsuppression rates between the 2 depressed groups.⁴¹

Other biological aspects of PMD have also been investigated. For example, PMD has been associated with a significant decrease in serum dopamine-beta-hydroxylase activity compared with controls, whereas NPMDs did not differ from controls⁴⁷ and with more rapid eye movement sleep disturbances compared with NPMD.⁴⁸ Structural and functional brain differences have also been found in PMD compared with NPMDs and healthy controls. A number of years ago, Rothschild et al¹⁰ reported enlarged ventricles in computer tomography in PMD patients compared with NPMD patients, an observation replicated by some groups⁴⁹ but not by others.⁵⁰ Some of these earlier samples combine unipolar and bipolar psychotic depressed patients, which may lead to some of these inconsistent biological findings.

Treatment Response

Treatment response has also been found dependent on depression subtype. Dubvosky⁵¹ concluded that about half of the depressed patients refractory to antidepressants have delusions and/or hallucinations of which the treating physician is unaware. Once, however, psychosis is detected, PMD patients still have different responses to the standard treatments. PMD is typically more difficult to treat than NPMD. Traditionally, it has been thought that electroconvulsive therapy (ECT) is more effective for PMD than for NPMD.^{52,53} The results for relapse rate after ECT between PMD and NPMD are more variable. Some have found that PMDs have a higher relapse rate than NPMDs,^{54,55} while others find no differences.⁵⁶ Prudic et al⁵⁷ found that, in a community setting, remission rates for full courses of ECT were 30.3%–46.7% and that relapse was more frequent in patients with PMD. That study was open label, thus almost certainly overstating treatment response. More recently, Birkenhager and colleagues^{58,59} found that among patients who had responded to ECT, those with psychotic depression relapsed less frequently than those with nonpsychotic depression. Tschiyama et al⁶⁰ tried predicting who would respond to ECT but did not find that the presence of psychotic features contributed to the variance. Thus, although ECT may be effective in initially treating psychotic depression, the data are unclear regarding the duration of this effect in psychotic depression.

Historically, tricyclic antidepressant monotherapy was thought to be relatively ineffective in PMD compared with NPMD, with the former requiring a combination of antidepressants and antipsychotics. It has been generally thought that serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors as monotherapy would be similarly ineffective. One group has reported unexpectedly higher rates of response on monotherapy with SSRIs, but these studies have not

been conducted under placebo-controlled conditions.^{61–63} More recently, Rothschild et al⁶⁴ examined the efficacy of olanzapine, placebo, or the combination of fluoxetine plus olanzapine in the treatment of PMD in 2 separate, parallel trials. In one trial, they found that, after 8 weeks of treatment, the group given combination therapy had greater improvement than did the group given placebo. In a second study, there were no significant differences in clinical outcome between the 3 treatment groups. Taken together, the combination separated from placebo first at 4 weeks and this difference continued out to 8 weeks. Although Howland⁶⁵ concluded that combining antidepressant and antipsychotic medications is the best approach if ECT is not used, this too remains uncertain. Interestingly, Rassmussen et al⁶⁶ conducted a retrospective review of ECT and prior medication use. They found that among patients with psychotic depression, 95% had been given an inadequate combination of an antidepressant and antipsychotic agent, mostly due to low doses of the latter class. Similarly, Andreescu et al⁶⁷ found that clinicians persistently use low doses of antipsychotics in the treatment of PMD. Thus, it is unclear whether ECT is truly more effective than drug therapy in PMD or whether patients are not adequately medicated. Overall, however, major depressive disorder (MDD) patients with psychotic features are clearly more difficult to treat effectively.

Overall, there are considerable data to indicate that psychotic depression is distinct from nonpsychotic depression in terms of clinical symptoms and course, biology, treatment response, and outcomes. However, there are inconsistencies among studies, and these measures may not be strong enough to be used in diagnosis. Thus, one could argue that more research is required before we adopt a designation of PMD as a separate disorder. Still the importance of psychotic features vis-a-vis clinical symptoms, course, and treatment in many studies does suggest that proper designation has a significant impact on outcome. Thus, whether one designates it as a separate disorder may be less important than developing better methods for delineating those patients with likely psychotic features to better guide care. Issues involved in this approach are described below.

Revamping the Current Diagnostic System

There are a number of issues that need to be considered even if one does not develop a separate designation for psychotic depression. First, in the current classification system, the presence of psychotic features is inexplicably linked to severity of depression. Second, the psychotic features' specifier is inadequately defined. What should be included—hallucinations or delusions only? What about cognitive disturbances such as odd thinking and poor cognitive function that are frequently observed, yet are not addressed, within the diagnosis? We believe

that going to a dimensional system of psychotic symptoms or cognitive disturbance that is not linked or dependent on severity would ultimately be more effective than the current binary classification of present or absent.

Psychosis vs Severity

In the current *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* classification of mood disorders, psychotic depression is described by a severity dimension specifier for major depressive episode, “severe with psychotic features.” There is no way to designate a mild or moderate depression with psychotic features. However, research has shown that the relationship of severity and psychosis is not that strong. Ohayon and Schatzberg⁵ reported that although the most severe forms of depression (as evidenced by meeting 8 or 9 of the 9 *DSM* depression criteria) were associated with higher rates of psychosis (33%), those with mild to moderate major depression also demonstrated relatively high rates of psychosis (15% and higher). Furthermore, they found that those with specific symptoms, particularly feelings of worthlessness and guilt, were most likely to have psychotic features; however, the severity of these 2 symptoms was not associated with the presence of psychotic features. In another recent study carried out in a large sample of patients with an index episode of major depression, Maj et al¹⁸ found that the index episode was more likely to be severe in patients with psychotic vs nonpsychotic depression but that in 23.6% of patients with psychotic depression the index episode was either mild or moderate. On the other hand, many severely depressed patients do not develop psychotic features.^{13,68} Thus, severity of depression alone does not entirely account for the presence of psychotic symptoms.

One recommendation to address this issue is to separate the dimensions of severity and psychosis. The severity dimension would continue to consist of 1 = mild, 2 = moderate, and 3 = severe, and a separate dimension would then take into account psychotic symptoms. The question then becomes: how do we characterize a dimension of psychosis? There are a number of ways in which this could be done. Above, we have reviewed the clinical and cognitive symptoms of psychotic depression. Below we discuss the clinical and cognitive symptoms of psychotic depression and how they may be incorporated into a psychosis dimension.

Psychotic and Cognitive Symptoms

Clinically, it is important to note that the boundary between psychotic and nonpsychotic symptoms is not always clearly delineated. Thoughts (or feelings) of guilt, worthlessness, deserved punishment, physical disease, poverty, and nihilism may be present in various degrees in depressed patients, with fluctuations within the same

episode. Maj et al¹⁸ found that, out of 452 patients with an index episode of major depression, 19.7% had at least one belief fulfilling both *DSM-IV* prerequisites for delusions, while 27.2% had no delusion but at least one sustained preoccupation, including 5.3% who met one of the *DSM-IV* prerequisites for delusions but not the other (ie, the belief was of “delusional proportions” but was not maintained with “delusional intensity”, or vice versa). How persistent the delusional quality must be in order to justify the diagnosis of psychotic depression is at present unclear. The same applies to hallucinations, which in several cases occur only occasionally, whose perceptual quality may be not straightforward and whose distinction from illusions (ie, misperceptions, colored by the depressed mood, of real sounds or voices) may be imprecise.

Guilt and feelings of worthlessness are 2 items that particularly fall into this category. For example, guilt is a common symptom of depression, and it may be best seen on a continuum of behavior rather than categorical present or absent. In many cases, the guilt may be beyond what is typically expected in depression but yet may not be fully delusional. A dimensional model of the psychotic specifier would account for such ambiguous symptoms.

The *DSM-IV* distinction between mood-congruent and mood-incongruent psychotic symptoms in depressed patients makes intuitive sense; however, there is little specific evidence for this distinction or its relevance. Mood congruence may be difficult to evaluate in some cases, and both mood-congruent and mood-incongruent symptoms may be present at the same time.^{18,69} In some studies, the presence of mood-incongruent psychotic symptoms in depressed patients was a predictor of a poorer outcome, but other studies did not replicate this finding.^{70,71} It would be advisable in the *DSM-V* to allow to record at the same time both mood-congruent and mood-incongruent psychotic symptoms or to use the expression “with predominant” mood-congruent or mood-incongruent psychotic symptoms. Further research is needed to understand the prognostic implications of these specific symptoms and the mood-congruent/incongruent psychotic distinction.

We propose that one way to assess psychosis is to develop dimensional ratings for specific psychotic as well as cognitive symptoms. One dimension could describe reality distortions from a mild UTC to frank delusions; another dimension would describe cognitive impairment which would encompass difficulties such as memory or concentration problems. Thus, one dimension would be used to assess psychosis/odd thinking/changes in reality with a scale from 0 = not present, 1 = vague, ideas of reference that are largely mood congruent, 2 = unusual thought patterns (not part of a delusion, not fixed thinking, or frequent illusions), 3 = subthreshold delusion, not quite fixed beliefs, and 4 = fixed, misperception of reality (fully delusional) or definite presence of hallucinations. The second dimensional scale could cover cognitive pro-

cesses/thinking. This dimension would likely be based on formal cognitive testing, which would encompass the domains which have been found to be impaired in PMDs, such as executive functioning, memory, and psychomotor speed. More research is necessary to determine which specific tests could be utilized in such a battery, and it would be necessary that such a battery is quickly and easily administered and has good sensitivity and specificity to psychotic depression. Here the ranges are less clear but could be rated as a scale from 0 = no cognitive impairment, 1 = impairment of 1 domain, 2 = impairment of 2 domains, and 3 = impairment of 3 domains, such that higher number indicates more domain impairment. For this dimension, we feel it would be important to have a short, standard battery to administer because very often depressed patients will have subjective cognitive complaints in the absence of quantitative deficits.

Relationship to Bipolar and Schizoaffective Disorder

A relationship between psychotic unipolar, major depression, and bipolar disorder has been repeatedly suggested on the basis of family history and risk of conversion.²⁸ There is considerable evidence to suggest that PMD is likely to represent a first episode of a bipolar disorder in younger patients. Because young patients often have less in the way of a history of mood problems, they may not have yet experienced the necessary hypomania or mania for a bipolar diagnosis at the time of their first depressive episode. For example, as noted above, Maj et al¹⁸ found that the switch to bipolarity was significantly associated with an earlier first psychiatric contact and a family history of bipolar I disorder but not with the presence of delusions in the index episode. Incidentally, many young, psychotic depressives do not convert to bipolar in a 10-year follow-up. It is clear that the issue of the overlap between PMD and bipolar disorder warrants further research attention in all the domains discussed above.

There is some difficulty distinguishing between psychotic depression and schizoaffective disorder, particularly in early episodes. In part, this occurs because the course and history of the depressive and psychotic symptoms are key to making an appropriate diagnosis. There is less history available in early episodes. Schizoaffective disorder tends to be chronic with a chronic thought disorder even when the patient is not depressed, whereas psychotic depression, including any thought disorder, is episodic. However, there are some similarities. As noted earlier, there is evidence to suggest that cognitive deficits in PMD may be more similar to but slightly less severe than those with schizoaffective disorder.³⁴ Furthermore, there is some evidence that long-term outcome for schizoaffective disorder patients is more similar to affective disorders than to schizophrenia.⁷² The potential overlap between PMD and schizoaffective disorder warrants further research attention.

Conclusions

In conclusion, currently available research evidence supports the usefulness of some “psychosis” specifier in the diagnosis of major depression. This specifier should be kept separate from the “severity” one. It should be possible to record the presence of both mood-congruent and mood-incongruent psychotic features in the same patient. More precise guidelines should be provided about how to distinguish psychotic from nonpsychotic experiences (eg, delusional from nondelusional guilt and hallucinations from illusions). These should highlight how persistent experiences need to be in order to justify a label of psychosis. Some biological findings could be acknowledged in the “Associated laboratory findings” section of the DSM, but the diagnostic criteria should be based on the clinical picture.

There are a number of research areas that could help address the needs laid out for psychotic depression categorization. First, it would be important to consider the definition of psychosis in the context of major depression. Does the definition need to be broadened to include cognitive distortions, not just full delusions? What are the primary delusions that occur in PMD? How should these be defined and what distortions are commonly seen in the context of MDD?

Formal thought disorder in severely depressed patients is understudied. The BPRS conceptual disorganization item is perhaps not optimal to explore this disorder because it is framed on the formal thought disorder of schizophrenia and is but one item. One characteristic of the formal thought disorder of depressed patients is that, contrary to what is assumed by the BPRS, its quality is not necessarily reflected by the degree of verbal production. For instance, a severely depressed patient with crowded or racing thoughts will often have a reduced (rather than increased) verbal production based on the nature of the mood component. Thus, we do not know whether, to what extent, or how formal thought disorder is manifest in major depression nor do we know its relationship to formal thought disorder in schizophrenia. More specific research in this area is warranted.

The *DSM-IV* distinction between mood-congruent and mood-incongruent psychotic symptoms in depressed patients makes intuitive sense. However, there is little specific evidence for this distinction or its relevance. It would be helpful to gather more data on the prevalence and importance of mood congruence in relation to prognosis, course, and outcome. Other issues to be investigated include: does having mood-incongruent psychotic symptoms put one at greater risk for relapse or a manic episode? Do those with mood-congruent psychotic symptoms have a better outcome than those with mood-incongruent symptoms?

A second important area of research is to develop a short neurocognitive battery that could help differentiate PMD from NPMD. Neurocognitive batteries can be

very complex and time consuming, and these would not be of benefit within a typical clinical practice. However, if a short battery could be developed to differentiate these patients with adequate sensitivity and specificity, it would be a very useful clinical tool. Starting with the neuropsychological findings to date, executive functioning, verbal memory, and psychomotor speed are the 3 areas which consistently are found to be impaired in PMDs. Issues that remain as problematic within the neuropsychology of PMD is that there are relatively few studies and medication status can be a factor.

A third issue for further study is whether any of the clinical, cognitive, or biological variables discussed above have diagnostic or prognostic value for psychotic depression. For example, do any of the specific psychotic or cognitive symptoms predict future PMD episodes or time to remission in the current episode? We already know that the presence of delusions and hallucinations in depressed patients does have some prognostic implications. Does the severity of the depressive episode (mild, moderate, or severe) also play a role in outcome? Psychotic episodes tend to have a longer duration and the recurrence rate tends to be higher. However, the medium- and long-term prognostic implications are less clear. In several studies, there was no significant difference in the outcome at 7 or 10 years between depressed patients with mood-congruent psychotic symptoms and nonpsychotic depressives. This may be in part due to the fact, reported by Winokur et al,⁷³ that psychotic symptoms tend to become less prominent late in the course of the illness. This finding, however, requires replication.

In addition, data suggest that the presence of delusions and hallucinations in depressed patients has therapeutic implications. Depressed patients with mood-congruent delusions and hallucinations are less likely to respond to antidepressant monotherapy than nonpsychotic depressives, but this is largely based on the tricyclic literature. However, the Italian data are highly suggestive of a potential benefit with SSRI monotherapy. This requires further controlled data.

There is some overlap between unipolar psychotic depression and bipolar disorder. A family history of bipolar disorder is significantly more frequent in depressed patients with mood-congruent psychotic symptoms than in nonpsychotic depressives, and we found that the percentage of patients with at least 2 manic symptoms in their index episode was significantly higher in the former.¹⁸ The prognostic and therapeutic implications of these findings should be further explored. Data on the familiarity of psychotic depression is also needed to better understand genetic influences. Furthermore, we do not have adequate data on cognitive and biological overlap of PMD and bipolar disorder, and this may warrant further investigation. Last, the clinical, biological, and treatment differentiation between PMD and schizoaffective disorder (depressed type) needs further study as well.

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