Psychotic Depression: An Evidenced Based Clinical Update

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To the faculty of Washington State University:

The members of the committee appointed to examine the clinical project of Nick J. Campo find it satisfactory and recommend that it be accepted.

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Abstract

This is an article based on an extensive literature review dealing with psychotic major depression, which is a relatively common subtype of depression that is easily misdiagnosed and therefore has the potential to be inadequately treated. The article is written for the target audience of primary care clinicians and outpatient psychiatric clinicians. The aspects of psychotic major depression that will be discussed are: clinical symptoms and diagnosis, prevalence and social characteristics, clinical course, familial history and genetic characteristics, neuropsychological aspects, biological aspects, and treatment. Suggestions for clinical practice are included.
**Introduction**

Psychotic depression is a relatively common subtype of Major Depression. It is a severe form of mood disorder characterized by delusions, hallucinations, psychomotor disturbances, increased feelings of guilt, and suicidal ideation. It is estimated that this form of depression affects 0.4% of the population (Keller et al., 2006). According to the DSM-IV-TR (American Psychiatric Association[APA], 2000), the lifetime risk for Non Psychotic Major Depression in community samples varies from 10% to 25% for females and from 5% to 12% for men.

Psychotic depression is easily mistaken for non-psychotic major depression and therefore can potentially be treated inadequately. Although the DSM-IV-TR (APA, 2000) criteria suggest that the essential difference between psychotic major depression (PMD) and non-psychotic major depression (NPMD) is the presence of delusions and/or hallucinations, many researchers have observed that the two syndromes are very distinct with different symptoms, clinical courses, familial patterns, cognitive changes, and biological features. The purpose of this article is to review the current knowledge base regarding the identification, clinical profile, and treatment of PMD in order to better inform APRN practice.

**Literature Review**

A review of the current literature on PMD revealed several focal areas of interest on the topic: clinical symptoms and diagnosis of psychotic depression, prevalence and social characteristics, clinical course, familial history/genetic characteristics, neuropsychological aspects, biological aspects, and the treatment of psychotic depression. These will be discussed and summarized in this article.
Clinical Symptoms and Diagnosis of PMD

The DSM-IV-TR (APA 2000) does not have any specific diagnostic criteria for PMD (see Appendix 1 for DSM-IV-TR criteria for a major depressive episode). In a study by Keller et al., (2006), the authors used the Brief Psychiatric Rating Scale (BPRS) (see Appendix 4) during patient interviews to differentiate between PMD and NPMD. The BPRS is an 18 item scale used to measure the severity of psychiatric symptomatology and has been used for decades as an outcome measure in treatment studies of various types of psychosis (Sadock & Sadock, 2007). The aim of the study was to assess whether individual or clusters of psychiatric symptoms could differentiate between PMD and NPMD. The authors studied 129 patients with major depressive disorder and determined that patients with psychotic depression were adequately differentiated by the Unusual Thought Content item of the BPRS. In a later article in 2007, Keller, Schatzberg, and Maj reported that any elevation, even a very small one, on the Positive Symptom Subscale of the BPRS (conceptual disorganization, suspiciousness, hallucinations, and unusual thought content) was even better at differentiating PMD from NPMD. Sensitivity and specificity for this scale were 84% and 99%, respectively. Ohayon and Schatzberg reported in 2002 that feelings of worthlessness or excessive guilt are a good indicator of psychotic symptoms in depressed patients.

Meyers et al., (2006) developed a scale to quantify and measure delusions in patients with psychotic depression. According to Meyers, “…the presence of delusions or hallucinations are critical to the diagnosis of major depression with psychotic features” (pg. 1336). Meyers goes on to state that hallucinations without accompanying delusions are rare in PMD, which highlights the importance of assessing and quantifying delusions in patients with PMD. The scale that the authors created is called the Delusion Assessment Scale and it is comprised of 15 items (see
Appendix 2). The Delusion Assessment Scale was administered to the 92 subjects enrolled in a study of pharmacotherapy for patients with PMD and the scores correlated significantly with BPRS Positive Symptom Subscale scores.

Similarly, Schatzberg and Rothschild (1992) stated that the hallmark feature separating PMD from NPMD is the occurrence of delusions and hallucinations in PMD. The delusions typically fall into the categories of guilt, paranoia, or somatization. Delusions are viewed as mood congruent if they reflect depressed mood via underlying nihilistic, guilty, or overly self-deprecating beliefs. Hallucinations are divided into auditory, visual and somatic subtypes. According to the authors, although psychotic depressions are often severe in nature, severity alone is not sufficient to differentiate PMD from NPMD. The authors do report that patients with PMD typically have greater psychomotor disturbance, feelings of guilt, and cognitive disturbance. In addition, patients with PMD tend to express more hopelessness, hypochondriasis, anxiety, and insomnia (early and middle); however these symptoms are less prominent and consistent when compared to psychomotor disturbance and guilt feelings. The authors also report that patients with PMD exhibit greater morbidity, including more frequent suicide attempts.

Rothschild (2003) also discusses the diagnosis of PMD. The author reports that the diagnosis of PMD cannot be made unless the clinician can detect the presence of delusions or hallucinations in the context of a major depressive episode (see Appendix 1). Rothschild also states that the psychotic symptoms can be present only in the context of the major depressive episode. Because the detection of delusions and hallucinations in depressed patients can be difficult, other characteristics can help detect PMD. Among those characteristics are, according to Rothschild, severe psychomotor disturbance, pronounced paranoid symptoms, cognitive
impairment, hypochondriasis, anxiety, insomnia (early and middle), and constipation. This author observed that patients with PMD do not exhibit a diurnal variation in mood when compared with severely depressed, non psychotic patients, meaning that patients with NPMD typically experience more severely depressed mood in the morning that improves as the day progresses, and patients with PMD tend to experience a severely depressed mood all day with little to no improvement as the day progresses.

In summary, PMD can be a difficult disorder to accurately quantify and diagnose. Excessive feelings or worthlessness and or guilt, as well as delusional thought content in general, can help the clinician to recognize PMD. Because PMD could be missed during the initial patient evaluation if the interviewer does not adequately question the patient about the presence of delusional thinking, the BPRS is helpful in establishing the diagnosis. In addition, the features of cognitive impairment, hypochondriasis, psychomotor disturbance, insomnia, and the absence of diurnal mood variation can help identify PMD. The following section will discuss the prevalence and social characteristics commonly observed in patients with PMD.

**Prevalence and Social Characteristics**

Ohayon and Schatzberg (2002) examined the prevalence of depressive episodes with psychotic features in the general population. The authors studied phone interview transcripts of 18,980 subjects residing in the UK, Germany, Italy, Portugal, and Spain. The study subjects were randomly selected and did not have to be engaged in any psychiatric treatment to be included in the study. The phone interviews were performed by trained lay interviewers who were prompted by the SLEEP EVAL computer program to ask the participants questions dealing with symptoms of depression as well as symptoms of psychosis. The authors concluded at the
end of the study that major depressive episodes with psychotic features are relatively frequent in the population, affecting approximately 0.4% of the population.

In an article written by Thakur, Hays, Ranga and Krishnan (1999), the authors examined the prevalence, demographic and social characteristics of PMD. The authors concluded that PMD is found in 25% of consecutively admitted depressed patients. This rate was also reported in Coryell, Plöhl, and Zimmerman, (1984), Wheeler, Mortimer, and Tyson, (2000), and Wijkstra, Lijmer, Balk, Geddes, and Nolan, (2006). Consecutive admissions may indicate more severe depression. In this study (Thakur et al., 1999), 674 patients with MDD were screened for delusions and hallucinations, in addition to age, gender, family history of suicide, lifetime history of bipolar diagnosis, psychomotor disturbance, guilt feelings, worthless feelings, presence of suicidal ideation, intent, and attempts, age at onset of first episode, vascular risk factors, and perceived social support.

Of the 674 patients studied by Thakur, et al., patients with PMD were twice as likely to be younger than 60, 66% more likely to be actively suicidal, and 50% more likely to exhibit psychomotor disturbance. Patients with PMD were 26 times more likely to have a past history of delusions, and because of this, a current episode of delusional depression, or PMD, could reasonably be considered predictive of delusional episodes in the future. Patients with PMD were also 66% more likely to be experiencing guilty feelings and were significantly more likely to be experiencing feelings of worthlessness. The authors also found a trend for PMD to be associated with Bipolar Disorder, in particular, younger patients with PMD were more likely to be diagnosed as Bipolar in the future when compared with NPMD patients. In addition, there was a trend for PMD to be associated with poor patient perceived social support, which is very important because studies have shown that social support, especially subjective or perceived
social support, is an important determinant of prognosis for depression. The sample was made up of 240 males and 434 females. 62 patients with PMD were male and 127 were female. 178 males met criteria for NPMD as did 307 of the females. The authors found that family history of suicide, age at onset of first Major Depressive Episode, and vascular risk factors were not significantly different between the PMD and NPMD patients. Of note, the authors report that vascular risk factors were sought by self report and that no clinical measures were used to define vascular risk.

Haim, Rabinowitz, and Bromet, (2006), examined the relationship of premorbid functioning and outcomes in first admission psychosis using the Premorbid Adjustment Scale. The group of 354 patients was made up of 177 patients diagnosed with Schizophrenia, 106 patients with Bipolar Disorder, and 68 patients with PMD. The authors found that poor premorbid functioning was associated with more severe negative symptoms at baseline, less improvement of negative symptoms, poorer overall clinical functioning, and poorer overall social functioning. The findings suggest that premorbid functioning may have prognostic implications in PMD as well as in Schizophrenia and Bipolar Disorder. Early detection of patients with poor premorbid functioning could enable utilization of more intense therapeutic services that may improve functioning. Treatment planning could be greatly improved by focusing more on premorbid functioning.

In summary, PMD is a relatively common disorder. It has been shown to be present in approximately 0.4% of the general population and has also been shown to be present in approximately 25% of patients with multiple inpatient psychiatric hospitalizations for depression. Patients with PMD tend to have a high incidence of poor patient perceived social support, as well as poorer overall outcomes when associated with poor premorbid functioning.
As stated previously, early detection of poor premorbid functioning would enable earlier utilization of more intense therapeutic services to help improve outcomes. The next section will discuss the clinical course of PMD.

**Clinical Course**

According to Rothschild (2003), patients with PMD experience more frequent relapses or recurrences than patients with NPMD. Also, patients with PMD exhibit increased use of services, greater disability, and poorer clinical course at short and long term follow up. Patients with PMD have a greater incidence of attempted suicides and total number of hospitalizations as well. The author also reported that patients who experience delusional thought content during their index depressive episode had a five fold increase in their likelihood of suicide when compared with patients without delusional thought content during their index episode. In addition, the authors report that individuals with PMD tend to demonstrate residual social and occupational impairment despite improvement in psychotic and mood symptoms at one, five and 10 year follow up.

Keller et al., (2007) found that patients with PMD often have longer duration of episodes and a greater likelihood of recurrence of depression. In addition, patients with a first episode of PMD tend to have future episodes of PMD. Tyrka, Price, Mello, Mello, and Carpenter (2006) had similar findings regarding a high interepisode consistency of psychotic symptoms, and also found a very low placebo response in people with PMD as compared to people with NPMD. According to Vythilingam et al., (2003), patients with PMD have a two fold increase in mortality when compared with NPMD patients. Vythilingam et al. followed 61 patients with PMD and 59 patients with NPMD for 15 years. The mortality rate for the individuals with PMD was 41% and
was 20% for the patients with NPMD. These findings held true after controlling for age and additional medical illness and were not due to elevated suicide rates. The authors report that the increased death rate was due to medical causes but they did not specify what the medical causes were. Only four patients with PMD committed suicide and all four suicides occurred within two years of the patients’ index episodes.

Schatzberg and Rothschild (1992) discussed a comparison of 52 patients with PMD versus 52 patients with NPMD at one year follow up after discharge from inpatient hospitalization. The PMD group had a significantly higher rate of depressive episodes lasting longer than nine months than did the NPMD group. The PMD group also was more likely to be in a major depressive episode at one year follow up. The author did not give specific details as to what method was used for patient follow up.

Naz et al., (2007) discussed findings regarding remission and relapse after the first hospital admission in patients with PMD. The authors followed 87 patients with PMD in Suffolk County, New York for four years after their first hospitalization for PMD. The authors found three consistent predictors of longer time to remission. The three factors were chronicity, the presence of mood incongruent delusions, and poor premorbid functioning.

To summarize, the clinical course of PMD involves more frequent relapses and recurrences, more frequent suicidal activity, less response to placebo, more frequent hospitalizations, and greater residual social and occupational dysfunction when compared with NPMD. Patients with PMD also tend to have longer depressive episodes, a greater likelihood of future psychotic episodes, and in one study, twice the mortality rate when compared with patients with NPMD. The next section will focus on the family history and genetics of people with PMD.
Familial History/Genetics

Tsuang, Taylor, and Faraone, (2004) performed a review of the psychiatric literature to determine the genetic underpinnings of psychotic mood disorders. The authors found that a large number of investigations had focused on psychotic depression but that it was unclear whether the relatives of patients with PMD were at a higher risk for either bipolar disorder or unipolar depression than were relatives of patients with NPMD. The authors found that relatives of patients with PMD are at higher risk for schizophrenia than relatives of patients with NPMD. The authors also found that when a distinction was made between mood-congruent and mood-incongruent psychotic symptoms in patients with PMD, the relatives of the PMD patients with mood-incongruent psychotic symptoms were at higher risk for schizophrenia and at lower risk for bipolar disorder.

According to Rothschild (2003), the first degree relatives of patients with PMD exhibit higher rates of PMD and NPMD than do the family members of NPMD patients. In one of the studies discussed by Rothschild, when PMD patients were divided by degree of HPA axis dysregulation (non-suppression of cortisol after being administered dexamethasone), the familial presence of depression was significantly higher in the families of PMD patients with high post-dexamethasone cortisol levels (> 15 mcg/dL) when compared with families of PMD patients with low or intermediate post-dexamethasone cortisol levels (0-14.9 mcg/dL). This finding, if replicated in further studies, could be used to focus prevention and early treatment efforts toward individuals with quantifiably higher rates of risk. In another study, the relatives of PMD patients were six times more likely to have Bipolar Disorder than were the relatives of NPMD patients (Weissman, Prusoff, and Merickangas 1984).
Coryell et al., (1984) described a study in which the relatives of patients with DSM-III PMD (47% of the patients had mood incongruent delusions) had a 1.1% incidence of schizophrenia. According to the authors, that figure was significantly higher than the 0.2% incidence of schizophrenia found in the family members of NPMD patients, but significantly lower than the 2.8% incidence of schizophrenia found in the family members of patients with schizophrenia.

Practitioners are advised to consider that relatives of patients with PMD are at higher risk for schizophrenia, PMD and NPMD than relatives of patients with NPMD. Other information from the literature suggests that prevalence of depression among relatives of people with PMD increases with the amount of HPA axis dysregulation in the person with PMD. The relatives of people with PMD also have a significantly higher risk of developing Bipolar Spectrum Disorder when compared with the relatives of people with NPMD. Bipolar Spectrum Disorder consists of Bipolar I, Bipolar II, Bipolar NOS and Cyclothymic Disorder (APA, 2000) The next section will discuss the neuropsychological aspects of PMD.

Neuropsychological Aspects

Hill, Keshaven, Thase, and Sweeney, (2004) examined neuropsychological dysfunction in antipsychotic naïve first episode unipolar psychotic depression. In their study, the authors administered a battery of neuropsychological tests to 20 individuals experiencing their first episode of psychotic depression before first exposure to antipsychotic medication. They administered the same battery of tests to 14 patients with NPMD as well as 86 patients diagnosed with schizophrenia spectrum disorder. The battery included tests of general intelligence, executive function, attention, verbal memory, visual memory, motor skills, and visual/spatial perception. The people with PMD performed more poorly in the areas of executive function,
verbal memory, visual memory, motor skills, and visual/spatial perception than the patients with NPMD. The patients with PMD actually scored slightly higher than the patients with NPMD in the area of attention.

Schatzberg et al., (2000) conducted a study in which a battery of neuropsychological tests was administered to 11 PMD patients, 32 NPMD patients, and 23 normal comparison subjects. The groups did not differ statistically in age, sex, or level of education. The authors found that the patients with PMD demonstrated significantly greater impairment than patients with NPMD and/or comparison subjects in attention and response inhibition as well as declarative memory.

Fleming, Blasey, and Schatzberg, (2003) discussed the neuropsychological correlates of PMD. The authors performed a meta-analysis of five studies dealing with PMD. The studies were included based on the availability of sample means and standard deviations so as to be able to calculate effect sizes, use of a NPMD control group, use of standard and reliable diagnostic procedures to confirm PMD, and use of standardized, reliable and valid neuropsychological tests. The studies looked at the neuropsychological areas of visual/spatial skills, attention, visual memory, verbal memory, executive functioning, and psychomotor speed. The authors found that when compared to patients with NPMD, patients with PMD demonstrated significantly large deficits in the domains of verbal memory, executive functioning, and psychomotor speed. These domains are largely mediated by the hippocampus and the prefrontal cortex, which indicates that these areas are affected in PMD and not NPMD. This will surely be an important target of future research in order to derive a more complete neurologic understanding of PMD.

Gaudiano and Miller, (2007) performed a study of the dysfunctional cognitions in hospitalized patients with PMD versus NPMD. Baseline data were pooled from two clinical trials in which 235 patients were recruited during a psychiatric hospitalization for an acute
episode. Twenty eight of the patients met criteria for PMD. The authors administered a battery of tests to each patient to measure depression, suicidality, hopelessness, social adjustment, dysfunctional attitudes and cognitive bias. PMD patients reported higher levels of common dysfunctional beliefs compared to NPMD patients. Higher levels of depressive cognitions were associated with greater social impairment and suicidality in PMD patients, even after controlling for depressive symptoms. PMD patients were also more likely to exhibit sustained and unvarying depressive thought content such as pessimism, sinfulness, and low self esteem. Study results showed that depressive cognitions were significantly related to poor social functioning in PMD patients. These findings suggest that Cognitive Therapies that target dysfunctional thinking patterns may be effective for PMD patients when used as an adjunct to pharmacotherapy.

Sommer, Veer, Wijkstra, Boks, and Kahn, (2006) described their findings regarding language lateralization differences in psychotic mania, PMD, and schizophrenia. The authors reported that the standard left asymmetry of the language areas (Broca’s Area mediates expressive speech and Wernicke’s area mediates language comprehension, both in the left brain hemisphere) in the human brain is decreased in schizophrenia patients as compared to controls. To investigate whether decreased language lateralization is a general characteristic of psychosis, the authors measured language activation with functional MRI in 14 patients with PMD, 13 patients with psychotic mania, 14 patients with schizophrenia, and 14 healthy controls. The groups were all matched for sex and all of the participants were right handed. Patients from all three of the diagnostic categories were in partial remission. The authors found that language lateralization is decreased in psychotic patients as compared to controls, regardless of diagnosis, which resulted from increased language related activation in the right hemisphere. This means
that these individuals demonstrated more generalized brain activity during MRI instead of more concentrated activity in the previously mentioned areas in the left hemisphere. Decreased lateralization was not related to the severity of the psychosis. This could suggest that decreased language lateralization may not fluctuate along with changing clinical symptoms, but perhaps remains stable over time. According to the authors, decreased lateralization is also present in non-psychotic monozygotic co-twins of patients with schizophrenia, which implies that decreased language lateralization reflects a genetic risk factor for psychosis, rather than a state related trait.

Gomez et al., (2006) performed a study of differences in neuropsychological functioning of PMD and NPMD patients from 2000 to 2006. The authors recruited 29 patients with PMD, 24 patients with NPMD, and 26 healthy controls from Stanford University Medical Center. No significant differences were found in the three groups in the areas of age, education, and premorbid estimate of intelligence. All of the subjects were admitted to Stanford University General Clinical Research Center and received structural and functional MRI, serial hourly blood testing for cortisol measurement over two days, and neuropsychological testing. The cognitive domains tested were premorbid intelligence, attention, working memory, semantic fluency, executive functioning, and verbal memory. The authors found that, in addition to having elevated mean cortisol levels from 1800 to 0100, the patients with PMD had significant cognitive deficits in the areas of working memory, psychomotor speed, immediate and delayed verbal memory, language and executive functioning. When compared to the patients with NPMD and healthy controls. Only simple verbal attention remained relatively unaffected in the patients with PMD. Verbal memory and executive functioning are believed to be mediated by the hippocampus and prefrontal cortex. These areas are also associated with impairment seen with
administration of exogenous glucocorticoids as well as with increased endogenous HPA activity, which is a consistently recognized aspect of PMD.

Patients with PMD demonstrate deficits in the areas of executive function, verbal memory, visual memory, motor skills, visual/spatial perception, attention, response inhibition and declarative memory when compared to patients with NPMD. In addition, patients with PMD exhibit more severe depressive thought content such as pessimism, sinfulness and low self esteem when compared to patients with NPMD, and these depressive cognitions are significantly related to suicidality and poor social functioning. Patients with PMD also demonstrate decreased language lateralization when compared with patients with NPMD.

Biological Aspects

Belenoff, Kalehzan, Sund, Fleming-Ficek, and Schatzberg, (2001) performed a study in which 10 patients with PMD, 17 patients with NPMD, and 10 healthy volunteers were administered the Wallach Memory Recognition Test (WMRT) and had blood drawn at 30 minute intervals over the course of an afternoon to assay cortisol levels. The subjects with PMD had a higher rate of errors on the WMRT and had higher cortisol levels throughout the afternoon than the subjects with NPMD and the healthy volunteers. The authors of the study concluded PMD is endocrinologically different from NPMD and produces cognitive changes that are distinct from those seen in NPMD. Similar conclusions were drawn by Gomez et al., (2005), Duval et al., (2006), Keller et al., (2006) and Thompson et al., (2006).

Stefos et al., (1998) performed a study to examine shortened REM latency as a psychobiological marker for psychotic depression. Forty four patients with PMD and 44 patients with NPMD were recruited. The two groups were matched for age, gender, and polarity, meaning there were equal numbers of patients with unipolar psychotic depression and bipolar
Psychotic depression. For both groups of patients, the authors examined TSH (thyroid stimulating hormone) response to thyrotropin releasing hormone, postdexamethasone cortisol levels, and electroencephalographic sleep characteristics. The studies revealed that the patients with PMD demonstrated increased nocturnal wakefulness, diminished REM latency, hypercortisolism, and blunted TSH response to thyrotropin releasing hormone, when compared to patients with NPMD. The increased wakefulness, thyroid axis, and HPA axis abnormalities seemed to be more related to depression severity than presence of psychosis, according to the authors. Shortened REM latency, however, was not influenced by depression severity and seemed to be more specifically related to the co-occurrence of psychotic and depressive symptoms.

Segal et al., (2006) performed a study looking at serum creatine kinase (CK) levels in unmedicated nonpsychotic, psychotic, bipolar and schizoaffective depressed patients. CK is an enzyme found in cardiac and skeletal muscle and in much smaller concentrations in brain tissue. CK is used in the diagnosis of myocardial infarction and is a reliable indicator of skeletal and inflammatory muscle diseases. CK levels may also rise in certain CNS disorders, such as Reye’s syndrome (Fischback 2000). The researchers recruited 109 consecutively admitted patients into the different adult psychiatric units at Mazra Medical Center in Acre, Israel. Of the recruited patients, 39 were diagnosed with NPMD, 23 with PMD, 23 with bipolar depression, and 24 with schizoaffective depression. The authors hypothesized that patients with NPMD would exhibit relatively lower CK levels when compared with patients with PMD, based on earlier studies in which patients experiencing psychosis related to schizophrenia or psychotic mood disorder had relatively higher CK levels when compared to patients with NPMD. All patients in this study met the DSM-IV-TR (APA, 2000) criteria for a major depressive episode, either recurrent or first
episode. All patients had a score of 14 or higher on the Hamilton Depression Rating Scale. All first episode patients were untreated at the time of the study. All patients with recurrent illness had been free of antidepressants and/or mood stabilizers for at least one month, oral antipsychotic treatment for at least three months, and depot antipsychotics for at least six months. Blood samples for serum CK were collected between 0800 and 0900 on the admission day, prior to any medication. CK levels were found to be significantly higher in the NPMD group than in all the other depression groups. Furthermore, there were no significant differences in CK levels between the PMD, Bipolar and Schizoaffective groups. These results seem to indicate a clear biological distinction between the NPMD and psychotic forms of depression. Based on this finding, the study authors suggest the existence of a psychotic depression cluster (PMD, bipolar depression, and schizoaffective depression) with different pathophysiologic traits than that of NPMD.

Contreras et al., (2006) performed a study regarding hormonal differences between psychotic and non-psychotic depressed patients, both with melancholia (see “definition of terms” section for definition of melancholia). The authors recruited 40 inpatients at the Hospital de Bellvige in Barcelona, Spain meeting the DSM-III criteria for a major depressive episode with melancholia, 19 with psychosis and 21 without psychosis. Each patient was administered the dexamethasone suppression test, the TSH response to Thyrotropin Releasing Hormone test, and the Growth Hormone response to Growth Hormone Releasing Factor test. In the whole sample, 80% of the patients had a disturbance in at least one of the axes, 40% in two axes, and 5% in all three axes. Basal and post-dexamethasone levels were significantly higher in the patients with PMD. In addition, an association was found between post-dexamethasone cortisol and blunted GH-GHRF response in the patients with PMD. Blunted TSH response was found in 25% of the
sample with no difference being found between PMD and NPMD groups. This study shows that hormonal disturbances in psychotic depression are more evident when studying several axes simultaneously.

Patients with PMD consistently demonstrate abnormal biological markers when compared with patients with NPMD. The most frequently demonstrated biological marker for PMD is elevated serum cortisol. Patients with PMD also demonstrate blunted GH-GHRF response and lower serum CK levels than patients with NPMD. Finally, people with PMD have been shown to demonstrate shortened REM latency, which has been shown to be specifically related to the co-occurrence of psychotic and depressive symptoms and not simply to depression severity. The next section will focus on the treatment of PMD.

Treatment

Pies (2003) reviewed selected articles dealing with different aspects of psychotic depression. The author stated that the traditional treatment approach for PMD has been a combination of an antidepressant medication and an antipsychotic medication. For the particularly severe or refractory cases the patient would receive ECT. The author stated that based on his literature review of 13 articles, antidepressant monotherapy would not produce adequate response and that monotherapy with a “typical” antipsychotic agent (see “definition of terms” section for definition of ‘typical antipsychotic’) would be ineffective. The American Psychiatric Association states in their Practice Guidelines for the Treatment of Psychiatric Disorders that PMD responds better to treatment with an antidepressant plus antipsychotic combination than to either component alone. They also recommend trying lithium augmentation for patients who have not responded to the antidepressant plus antipsychotic combination therapy.
Psychotic Depression: An (American Psychiatric Association [APA], 2002, 497). The article does not mention why the author chose the articles that he used for his literature review.

Pies (2003) said that monotherapy with an atypical antipsychotic agent such as risperidone or olanzapine may relieve both the depressive and psychotic symptoms of psychotic depression. Currently, according to Pies, the accepted best practice for treating PMD is a selective serotonin reuptake inhibitor (SSRI) or a serotonin norepinephrine reuptake inhibitor (SNRI) antidepressant plus an atypical antipsychotic agent. According to the author, most patients with PMD may be slowly tapered off the atypical after at least four months of therapy but should remain on the SSRI/SNRI for at least six to 12 months before being slowly tapered. If at any time during the taper of either drug there is PMD symptom exacerbation the patient should be placed back on the doses of the initially effective medications.

Flores, Kenna, Keller, Solvanan, and Schatzberg, (2005) performed a study in which 30 patients with PMD were treated with either Mifeprestone 600 mg per day for eight days or placebo for eight days in a randomized, double-blind manner. The Hamilton Depression Rating Scale (HDRS) and BPRS were administered at baseline and after eight days of treatment. Cortisol and adrenocorticotropic hormone (ACTH) were measured hourly from 1800 to 0900 at baseline and after eight days of treatment. More patients in the Mifeprestone group (7/15) showed a 50% or greater decline on the BPRS as compared to the placebo group (2/15). Similar results were achieved by DeBatista, et al., (2006). This indicates that Mifeprestone may be an effective treatment for some patients with PMD.

Andreescu et al., (2006) performed a study on 100 patients with PMD looking at the pharmacotherapy they received under “real world”, non-study conditions. The treatments were assessed before the patients were randomized into the Study of the Pharmacotherapy of
Psychotic Depression (STOP-PD). The authors used the Antidepressant Treatment History Form (ATHF) to rate the strength of antidepressant trials and used a modified version of the ATHF to rate the strength of antipsychotic trials or combinations of antidepressants and antipsychotics. They also determined whether the strength of antipsychotic or combination trials was associated with age, duration of the current episode, medical burden, cognitive status, or severity of depressive or psychotic symptoms. The authors found that 82% of the patients were treated with antidepressants and 65% with antipsychotics. Forty eight percent of the patients received therapeutic doses of antidepressants. Ten percent and 6% received intermediate and high doses of antipsychotics, respectively. Overall, only 5% of the patients received a combination of an adequate dose of antidepressant and a high dose antipsychotic. The strength of both antipsychotic and combination trials was significantly associated only with a longer duration of the current depressive episode. These findings show a persisting low use of antipsychotics in the treatment of PMD. This goes against the currently accepted practice guideline of using a combination of an adequate dosage of an antidepressant and a high dose antipsychotic for at least four to six months.

Wijkstra et al., (2006) described a systematic review and meta-analysis of 10 randomized placebo controlled trials of antidepressant monotherapy, antipsychotic monotherapy, and combination therapy for the treatment of unipolar psychotic depression. According to the authors, they found no evidence that the combination of antidepressant with an antipsychotic is more effective than an antidepressant alone. They did find that an antidepressant plus antipsychotic combination is more effective than an antipsychotic alone. Their final conclusion was that antidepressant monotherapy with the addition of an antipsychotic if the patient does not respond, or starting with an antidepressant plus antipsychotic combination both appear to be
appropriate when treating PMD patients. They did state that clinically, the balance between risks and benefits may suggest that initial antidepressant monotherapy may be preferred for many patients. The authors concluded that starting with an antipsychotic alone appears to be inadequate for treating PMD.

Konstantinidis et al., (2006) performed a six week, multicenter open label evaluation of quetiapine (up to 750mg per day, minimal dose permissible 50 mg per day) in combination with citalopram (20-60 mg per day, minimum dose permissible 20 mg per day) in 25 patients with unipolar PMD. The patients ranged in age from 18 to 70, and all had a HAM-D-21 (21 Item-Hamilton Depression Rating Scale) score of >25 (mean 31.21 +/-5.18). Each patient received citalopram 20 mg on day one with flexible titration based on tolerability up to 60 mg per day after two weeks. Quetiapine was administered in bid dosing, beginning with 50 mg on day one and up to 200mg on day 4. From day 5 quetiapine was flexibly titrated according to clinical response and tolerability up to a maximum of 750 mg per day, with a recommended dose of 100-200 mg per day. Other antidepressants and antipsychotics were prohibited. As a group, the patients received a mean daily quetiapine dose of 303 mg +/- 118 and a mean citalopram dose of 34 mg +/- 12. The group experienced a HAM-D-21 change of 31.21 +/-5.18 to 13.25 +/-10.87 at the end of six weeks. In addition, the group had a BPRS mean of 59.25 +/-6.60 at baseline and a mean of 35.25 +/- 15.60 at the end of six weeks. These results, in addition to the FDA indication for monotherapy treatment of bipolar depression for quetiapine, suggest that it may be useful to further evaluate the efficacy of quetiapine monotherapy in unipolar PMD.

Goto et al., (2005) performed a study assessing risperidone in the treatment of psychotic depression and examined the mechanism of risperidone to ameliorate psychotic depression. They recruited 15 patients with current unipolar psychotic depression and five patients with
bipolar disorder, current episode depressed, with psychotic features. There were eight males and 12 females with a mean age of 54 +/-18. All patients’ baseline status and improvement were evaluated using the HAM-D and PANSS (the Positive and Negative Symptom Subscale). In addition, plasma concentrations of HVA (homovanillic acid) and MHPG (3-methoxy-4-hydroxyphenylglycol) at baseline were determined for each patient. HVA is a metabolite of dopamine and MHPG is a metabolite of norepinephrine (Kaplan & Saddock, 2005). Patients with a >/= 50% improvement in HAM-D were considered responders. Three were prescribed risperidone alone, and the other 17 were administered risperidone as an addition to preexisting antidepressants or mood stabilizers such as Paxil, lithium, Depakote, Anafranil, Luvox, Elavil and Ascendin. The average dose of risperidone was 1.8 +/-0.5 mg per day. Fifty five percent of the patients (11 of 20) turned out to be responders four weeks after initiation of risperidone. No differences were observed between responders and nonresponders with respect to age, sex, HAM-D score before risperidone treatment, dose and plasma level of risperidone or its active metabolite paliperidone. Plasma HVA levels before risperidone treatment in responders were significantly higher than those in nonresponders. In addition, there was a significant correlation observed between changes in plasma HVA level and the percentage improvement on HAM-D score. There was not an association between MHPG levels and response to risperidone. These results indicate that in this study, treatment with risperidone is effective to ameliorate psychotic depression in certain patients, and the influence of risperidone on dopaminergic activity is associated with its efficacy. While medications are usually the first choice for the treatment of PMD, they are not the only choice.

ECT is also an effective treatment for PMD. In a study conducted by Birkenhager, Van den Bock, and Mulder, (2005), the authors studied the one-year outcome of patients with
psychotic depression after successful ECT. In the study, 59 patients who were considered responders to ECT were followed for one year. Twenty nine of the patients had PMD and 30 had NPMD. Relapse was defined as meeting DSM-IV-TR criteria for major depressive disorder and a HAM-D score of $\geq 16$. The frequency of relapse after four and 12 months was compared between both samples, adjusted for the covariables of index episode duration and type of post ECT pharmacotherapy. At both four and 12 months after ECT, instances of relapse were significantly lower in patients with psychotic depression compared with nonpsychotic patients: 3/28 (11%) versus 16/27 (59%) and 4/27 (15%) versus 19/28 (68%), respectively. These results demonstrate the favorable four month and one year outcome for patients with PMD after response to ECT.

Although there are no absolute rules for treating PMD, the literature does provide some evidenced based interventions. Commonly prescribed antidepressants such as the SSRIs and SNRIs have been shown to be an appropriate initial treatment for PMD, as have tricyclic antidepressants (Bruijn, Moelman, Mulder, and Van den Bock, 2001). There is also evidence to support beginning treatment with an antidepressant plus atypical antipsychotic combination and slowly tapering the antipsychotic after at least four months after remission and then attempting antidepressant taper six to twelve months after remission. There are even studies that demonstrate the safety and efficacy of certain atypical antipsychotics as monotherapy for PMD. Multiple studies have demonstrated the efficacy and safety of short term treatment of glucocorticoid receptor antagonists such as mifepristone for PMD. Unfortunately, mifepristone is not FDA approved for PMD and is a controversial medication due to its other use for early pregnancy termination and is very strictly controlled for that purpose. Because of that, it may be politically difficult to achieve FDA approval of mifepristone for PMD. ECT has been shown to
be a very safe and effective PMD treatment, but due to it being a procedure which requires
general anesthesia with a relatively small number of specially trained psychiatrists and facilities
to provide it, it generally remains an option only after multiple well documented medication trial
failures.

The information gained from this extensive literature review supports treating the patient
with PMD that presents to primary care with an initial combination of an SSRI and an atypical
antipsychotic, both at fully optimized dosages, for at least four to six weeks, in collaboration
with a psychiatric specialist (psychiatrist or psychiatric nurse practitioner). The choice of what
particular antidepressant plus antipsychotic combination would have to depend on several factors
such as patient preference, patient allergies and medical status, history of past response/non-
response to previous medications, past medication side effects, and prescriber familiarity/
comfort with individual medications. If the patient does not respond to the initial antidepressant
plus antipsychotic combination, this author recommends that the patient be referred to a
psychiatric specialist, if available, for further treatment. Once the patient is under the care of the
psychiatric specialist, the literature still recommends at least one to two more different
antidepressant plus antipsychotic combinations, each fully optimized for at least four to six
weeks. If the patient’s psychotic depression still has not responded, the psychiatric specialist
should consider referring the patient for inpatient hospitalization and/ or ECT. Of course, if the
patient’s condition ever deteriorates to the point where there is concern that the patient is gravely
disabled or is a danger to self or others, the patient should immediately be referred and/or
escorted to the nearest emergency department for inpatient psychiatric hospitalization.


Haim, R., Rabinowitz, J., & Bromet, E. (2006, October). The relationship of premorbid functioning to illness course in schizophrenia and psychotic mood disorders during two


Appendix 1 DSM-IV-TR Criteria for a Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either

(1) depressed mood or
(2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

(1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).

Note: In children and adolescents, can be irritable mood.

(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)

(3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.

Note: In children, consider failure to make expected weight gains.

(4) Insomnia or Hypersomnia nearly every day

(5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

(6) fatigue or loss of energy nearly every day

(7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

(8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a Mixed Episode (see p. 335).

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.
## Appendix 2: Delusion Assessment Scale

<table>
<thead>
<tr>
<th>Scale Items</th>
<th>Impact</th>
<th>Disorganization</th>
<th>Conviction</th>
<th>Bizarreness</th>
<th>Extension</th>
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<tr>
<td>Temporal pressure</td>
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<td>Acting on the belief</td>
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<td>Temporal pressure during interview</td>
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<td>Acting irrationally distrustful during the interview</td>
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<td>Emotional pressure</td>
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<td>Cognitive integration</td>
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<td>Internal consistency</td>
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<td>Temporal continuity</td>
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<td>Accommodation</td>
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<td>Subjective feeling of certainty</td>
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<td>Relationship to cultural context</td>
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<tr>
<td>Implausibility/bizarreness</td>
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<td>Places/situations involved</td>
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<tr>
<td>People/objects involved</td>
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</table>
## Appendix 3 Brief Psychiatric Rating Scale

### Instructions

This form consists of 24 symptom constructs, each to be rated in a 7-point scale of severity ranging from 'not present' to 'extremely severe'. If a specific symptom is not rated, mark 'NA' (not assessed). Circle the number headed by the term that best describes the patient's present condition.

<table>
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<th>5</th>
<th>6</th>
<th>7</th>
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<td>12</td>
<td>Bizarre behavior</td>
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<td>posturing</td>
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Appendix 4 Definition of Terms

Major Depressive Episode- feeling sad or having markedly diminished interest in activities that usually bring pleasure more days than not for at least 2 weeks. These two symptoms must be combined with at least four of the following symptoms: decreased weight, appetite change, sleep change, psychomotor change, decreased energy, feelings of worthlessness or guilt, impaired concentration, and preoccupation with death (The American Psychiatric Association, 2000).

Depression- “psychopathological feeling of sadness” (Sadock & Sadock, 2003, p. 280).

Psychosis- “loss of reality testing and impairment of mental functions manifested by delusions, hallucinations, confusion, and impaired memory. The inability to distinguish reality from fantasy” (Sadock & Sadock, 2003, p. 276, p. 282).

Major depression with psychotic features (psychotic depression)- a depressive episode that meets all the criteria for major depression with some form of psychosis such as delusions or hallucinations(Sadock & Sadock, 2003).

Melancholic Features- either of the following, occurring during the most severe period of the current depressive episode: loss of pleasure of all or almost all activities or lack of reactivity to usually pleasurable stimuli. Three or more of the following must also be present: 1. distinct quality of the depressed mood such that it is distinctly different from the kind of feeling experienced after the death of a loved one, 2. depressed mood consistently worse in the morning, 3. early morning awakening (at least two hours before usual time of awakening), 4. marked psychomotor retardation or agitation, 5. significant anorexia or weight loss, 6. excessive or inappropriate guilt (Sadock & Sadock, 2003)
Mood-congruent delusion- a delusion with mood-appropriate content (e.g. a depressed patient believes that he or she is responsible for the destruction of the world) (Sadock & Sadock, 2003, p. 283).

Mood-incongruent delusion- a delusion with content that has no association to mood or is mood neutral (e.g. a depressed patient has delusions of thought control or thought broadcasting) (Sadock & Sadock, 2003, p. 283).

ECT- electroconvulsive therapy.

Typical antipsychotics- medications used to treat psychosis since the 1950's. These are also known as dopamine receptor antagonists. These medicines are effective but cause many unwanted side effects. Examples of these medicines are haloperidol, chlorpromazine, and loxapine (Sadock & Sadock, 2003, p. 497)

Atypical antipsychotics- medications also used to treat psychosis. This group consists of six drugs: clozapine, risperidone, olanzapine, quatiapine, ziprasidone, and aripiprazole. These medications are also known as serotonin/dopamine receptor antagonists. They cause fewer side effects than do the typicals and are more effective (Sadock & Sadock, 2003, p. 497).

Mifepristone- a glucocorticoid receptor antagonist medication.

BPRS-brief psychiatric rating scale.