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An Update on Psychotic Depression

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1. Introduction

There has been a debate since the 1980's whether delusional depression or psychotic depression is a distinct psychiatric disorder. (Glassman & Roose, 1981) Currently, DSM-IV-TR classifies psychotic symptoms in patients with major depressive disorder as a severity specifier. However, researchers in the area of major depressive disorder, with psychotic features (PMD) believe that PMD is a distinct disorder based on not only the phenomenological presentation, but family studies, course of illness, biological findings, and treatment as well. This lack of recognition of PMD as being a distinct disorder has contributed to the limited amount of research funding for this disorder in spite of a prevalence in the general population of 0.4-0.6%. (Johnson et al., 1991; Ohayon and Schatzberg, 2002) This chapter will provide an update on studies that support PMD as being a distinct psychiatric disorder.

2. Phenomenology of PMD

The DSM-IV-TR definition of PMD is major depressive disorder plus delusions or hallucinations. Early studies report that delusions occur in one half to two-thirds of adults and hallucinations occur alone in 3-25%. However, in our more recent studies, delusions co-occur with hallucinations in as many as 67% of patients with PMD. (Matthews 2002, 2008) The most common delusions include: persecution, suspiciousness, paranoia, sin, guilt, ideas of reference, and somatic. (Frangos et al, 1983) Fifty percent or more experience more than one kind of delusion. (Dubovsky, 1992) Keller (2006) reported that patients with PMD score higher on unusual thought content, psychomotor retardation, and guilt than NPMD. Interestingly, a formal thought disorder occurs in only 20% of patients with PMD, thus, psychotically depressed patients who present with a formal thought disorder are more likely to have a diagnosis of either bipolar disorder or schizophrenia. The most common hallucinations are auditory and visual and they occur with equal frequency. (Schatzberg and Rothschild, 1992) Tactile and olfactory hallucinations may occur but usually with other types of hallucinations. In one study, olfactory hallucinations occurred in 40% of PMD patients. (Matthews et al., 2002) Dissociative symptoms in the absence of abuse may occur with greater frequency in PMD than NPMD. The psychotic symptoms of PMD may present as mood congruent or mood incongruent. In a study of 40 PMD inpatients, 26 (65%) had mood congruent (MC) and 14 (35%) had mood incongruent (MI) psychotic symptoms; 71% of patients with MC experienced at least 1 MI symptom and 50% of patients with MI experienced at least 1 MC

psychotic symptom. (Burch et al., 1994) In a 10-year study by Maj et al. (2007), 10% of 452 PMD patients had both MC and MI psychotic symptoms. Having MC or MI or both does not predict response to treatment or prognosis. (Rothschild, 2009)

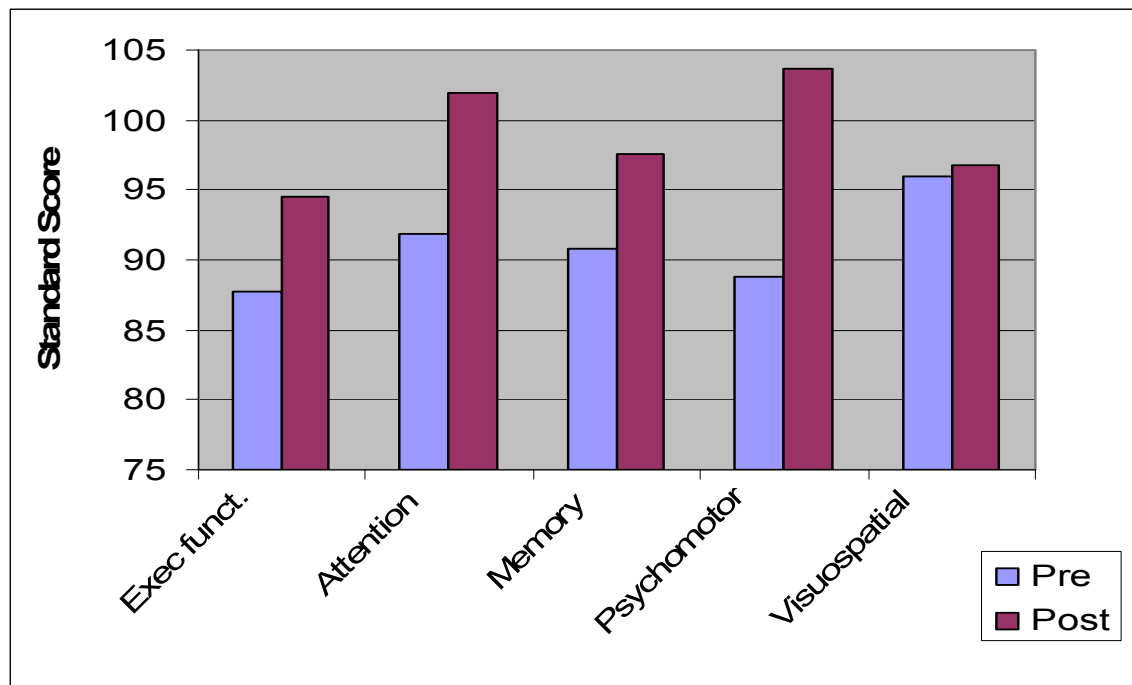


Fig. 1. (Matthews et al., 2010)

As with schizophrenia and bipolar disorder, patients with major depressive disorder exhibit cognitive deficits as a part of their clinical presentation. However, patients with PMD show greater performance deficits on specific neuropsychological tasks than patients with major depressive disorder, without psychotic features (NPMD). (Gomez et al., 2006) In addition, patients with PMD demonstrate more difficulty processing, manipulating and encoding new information than patients with NPMD (Gomez et al., 2006) In a meta-analysis of five studies, Fleming et al. (2004) showed that patients with PMD scored significantly lower on neuropsychological measures of executive function, verbal memory, and psychomotor speed than patients with NPMD.

We also found that patients with PMD scored significantly lower on executive function, verbal memory, and psychomotor speed than patients with NPMD. (Figure 1) (Matthews, et al., 2010) The mean scores on these three measures for PMD were greater than one standard deviation below the mean for the general population. The total score on the BPRS predicted the lower scores on executive function, verbal memory, and psychomotor speed, whereas, the HAM-D-17 did not. We also found that these cognitive deficits significantly improved with remission of PMD; thus, the cognitive deficits were state dependent (Table 1).

In order to control for the possible impact of medications on cognitive function, Hill et al., (2004) studied first episode PMD, Schizoaffective, Schizophrenia versus NPMD and healthy controls. There were significant differences between PMD and NPMD on several neuropsychological tasks; however, PMD was more similar to, but less severe, than performances by first break schizophrenics. (Figure 2) Hill hypothesized that the cognitive deficits found in PMD and schizophrenia may involve similar brain systems.

• Executive function
- Pre -Treatment 87.76 (±18.89)
- Post -Treatment 94.52 (±15.58) *
• Memory
- Pre-Treatment 90.85 (±10.87)
- Post- Treatment 97.57 (±14.36)
• Psychomotor
- Pre-Treatment 88.82 (±30.51)*
- Post-Treatment 103.77 (±25.39) *

* p < .01

Table 1. (Matthews, et al., 2010)

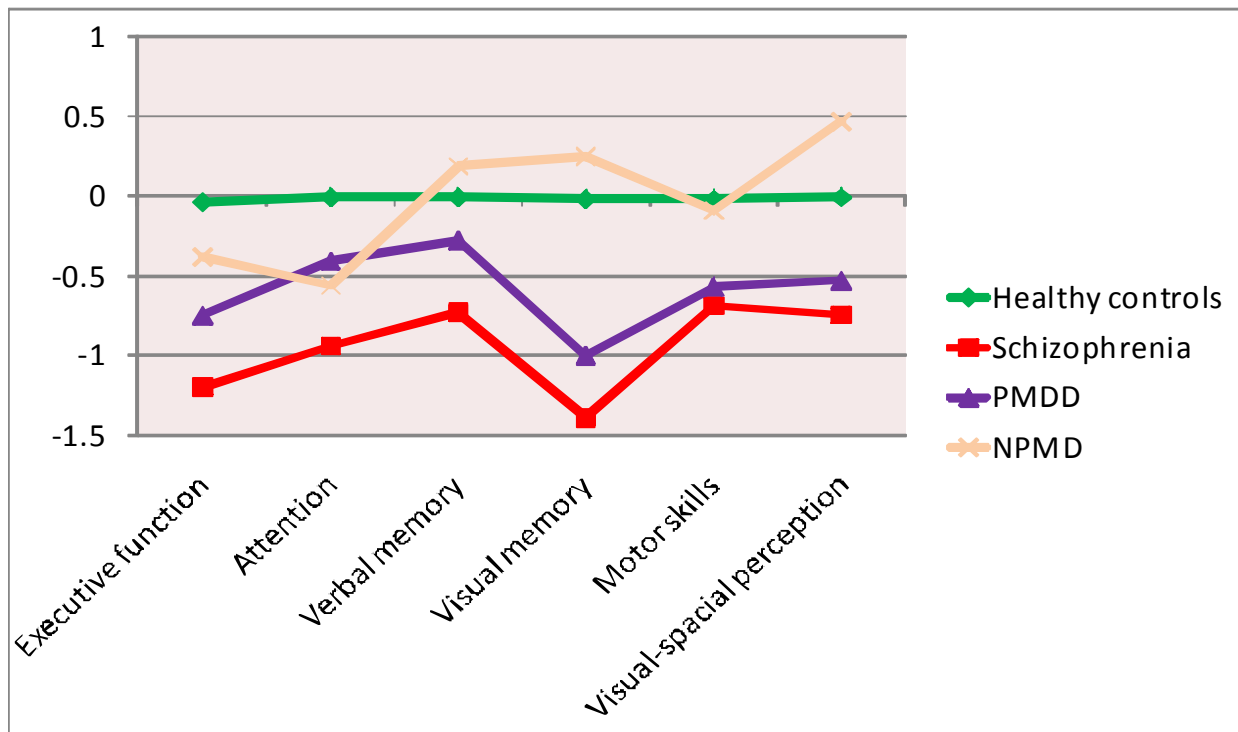


Fig. 2. (Hill et al., 2004; adapted)

3. Differential diagnoses

The diagnosis of PMD is often missed. Rothschild et al., (2008) found that in the NIMH Study of Pharmacotherapy of Psychotic Depression (STOP-PD), which was located at 4 academic medical centers, only 65% (85/130) of clinicians made an accurate diagnosis. Missed diagnoses on inpatient units were significantly less than in the emergency room; 18% (13/74) versus 39% (22/56) ($\chi^2=7.64$, $p<.01$) respectively. Distinctions between PMD and schizoaffective disorder or bipolar disorder are most problematic. In schizoaffective disorder, psychotic symptoms are not confined to mood disturbance, whereas, in PMD, psychotic symptoms co-occur with symptoms of depression. However, Maj et al., (2007) found that 10% of PMD with mood incongruent psychosis met criteria for schizoaffective

disorder, depressed type. Studies have shown that a subset of patients with PMD eventually experience a manic or hypomanic episode. This is particularly true for early onset PMD. Between 40-75% of adolescents with PMD convert to bipolar disorder (Askiskal et al., 1983; Strober and Carlson, 1982). Maj et al., (2007) found a switch rate of 10.1% for PMD versus a switch rate of 5% for NPMD in an adult population (n=452) over a 10-year period.

4. Family studies/genetics

There is limited data to support PMD as being a genetic disorder. In the case of NPMD, twin studies have demonstrated that there is a genetic factor that is passed on from one generation to the next. In a review of twin studies in NPMD, Sullivan and Kendler (2001) estimated heritability to be 37%, with a significant component of individual environmental risk. Brown et al., (1994) found that only 20% of patients with PMD could identify a significant stressor in the 6 month period prior to a new episode onset compared to 72% in patients with NPMD. These results might reflect differences in the procurement of homogeneous populations or the genetic loading or both. Rothschild (2009) summarized the family studies of first degree relatives comparing PMD and NPMD and found that the first degree relatives of PMD had higher rates of PMD, higher rates of bipolar disorder by a factor of 6 (Weissman et al., 1984), higher rates of cyclothymia in children by a factor of 3 (Weissman et al., 1988), and higher rates of NPMD if PMD probands had a post-dexamethasone serum cortisol of >15 ug/dl (Bond et al., 1986). A number of candidate genes have been proposed including genes for: dopamine- β -hydroxylase (DBH); dopamine D4 receptor gene; glycogen synthase kinase-3 gene; and serotonin transporter gene (5-HT1A; 5-HT2C; 5-HT 2A receptor gene). The gene for the DBH activity has been most promising based on the findings that five of six studies have shown decreased DBH activity in PMD. (Rothschild, 2009) Schatzberg et al., (1985) have hypothesized that a decrease in DBH enzyme activity may be important as to why depressed patients may become psychotic; reduced DBH activity results in a decrease in conversion of dopamine to norepinephrine thus increasing the availability of dopamine. The gene encoding DBH is located on chromosome 9q34; the adenosine allele predicts psychosis. (Craig et al., 1998; Wood et al., 2002)

5. Comorbidity

There is very little literature on the co-morbid psychiatric disorders in PMD. In a clinical trial of the combination of olanzapine plus fluoxetine, Matthews et al., (Figure3) found that anxiety disorders were among the most common; especially panic disorder.

6. Biology of PMD

Although there have been a few EEG and imaging studies using CT and MRI scans in depression, the most consistent findings have been with the dysregulation of the hypothalamic-pituitary-adrenal axis (HPA-axis). Table 2 summarizes the findings.

Researchers have known since the 1970's that cortisol is elevated in patients with NPMD (Carroll et al. 1981; Brown et al., 1985); however, the dysregulation of the HPA-axis is even more pronounced in PMD. Twenty-four hour urinary free cortisol is significantly higher in PMD than in NPMD and patients with PMD also have higher rates of dexamethasone

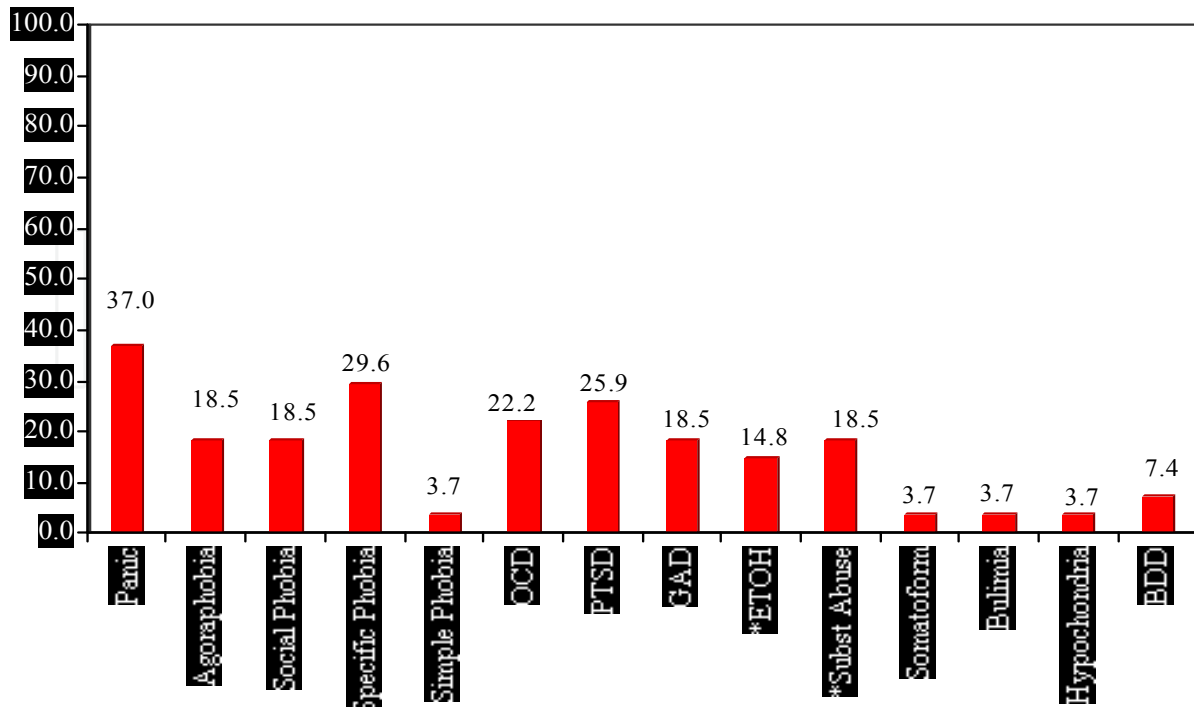


Fig. 3. (Matthews et al., 2002)

- ↑ cortisol in urine, blood, and CSF
- ↑ cortisol response to ACTH
- ↑ size of both pituitary and adrenal glands
- ↑ secretion of CRH
- ↑ CRH in CSF
- ↑ CRH messenger RNA in PVN
- ↑ ACTH response to CRH challenge

Table 2. Evidence for HPA-axis Hyperactivity

stimulation test (DST) non-suppression than patients with NPMD. (Nelson and Davis, 1997; Schatzberg et al., 1992) The presence of psychotic symptoms accounts for most of the variance and severity of depression does not account for the differences. (Schatzberg et al., 1992) In a meta-analysis of 14 studies (12/14 inpatient), the DST non-suppression rates were 64% for PMD (n=276) and 41% for NPMD (n=708) (p<0.001) with a sensitivity of 64% and specificity of 59% using a post-dexamethasone cortisol serum level cut off of ≥5 ug/dL. (Nelson & Davis, 1997) These differences between PMD and NPMD DST non-suppression appear to be due to the presence of psychosis since Nelson and Davis, in another meta-analysis of 19 studies of NPMD, showed that there were no significant differences in DST non-suppression rates of inpatients with or without melancholic features; the rates were 38% versus 33% respectively (p=0.74) The DST non-suppression rate for non-melancholic outpatients (n=138) was 12%. Using a cut off for DST non-suppression of ≥15 ug/dL, Schatzberg et al., (1983) improved on the specificity (93%) but, not on the sensitivity (50%) of DST. Rothschild et al., (1982) demonstrated that the DST distinguished PMD from schizophrenia; the DST non-suppression rate for PMD was 57% and 0% for psychotic

schizophrenics. The dysregulation of the HPA-axis is a state rather than a trait phenomenon. There is normalization of the HPA-axis with treatment (Carroll et al., 1981). Using the combined DST and corticotropin releasing hormone (CRH) infusion test, Kunugi et al. (2006) reported significant decreases in ACTH ($p=.007$) and cortisol ($p=.002$) levels with response to treatment in patients with PMD.

The mechanism for the hyperactivity of the HPA-axis is based on studies that suggest glucocorticoid-mediated feedback impairment at the level of the pituitary and hypothalamus. (de Kloet et al., 1998; Young et al., 1991) Specifically, glucocorticoid receptors are located in the cytoplasm of cells and consist of two types, GR I and GR II. The GR I receptors are the high affinity receptors for endogenous glucocorticoids and are responsible for the diurnal regulation of cortisol; whereas, the GR II receptors are the low affinity glucocorticoid receptors and are important when cortisol levels are high, such as in stress or depression. It is hypothesized that, in depression, there is an impairment in the translocation of the glucocorticoid receptor from the cytoplasm into the nucleus; once activated by cortisol, the glucocorticoid receptor translocates in to the nucleus to complete the feedback by binding to DNA. (Figure 4; adapted) (Parionte and Miller, 2001; adapted) Interestingly,

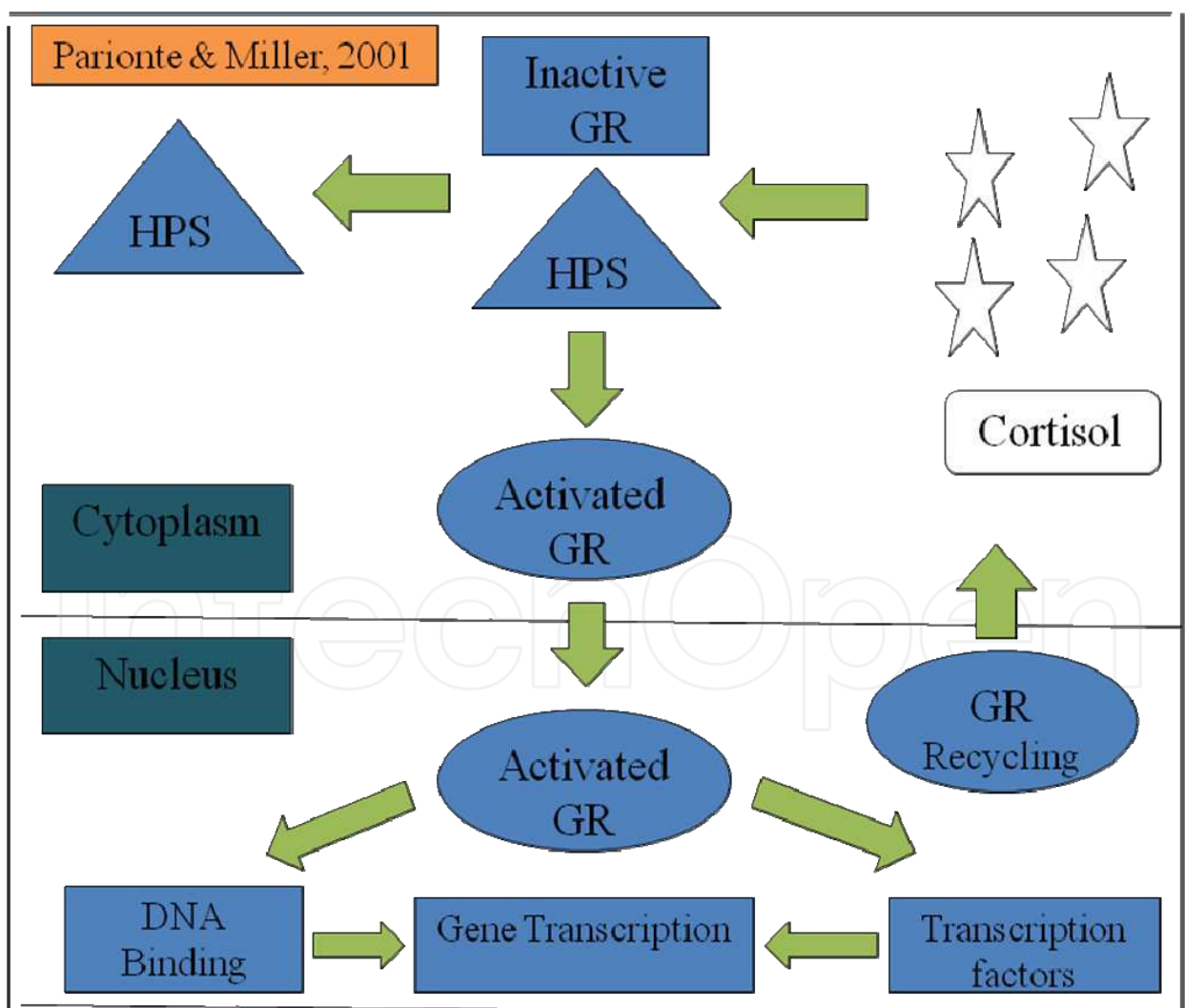


Fig. 4. (Parionte & Miller, 2001; adapted)

preclinical studies have shown that serotonin re-uptake blockers (SSRIs) and tricyclic antidepressants (TCAs) facilitate the translocation of the activated glucocorticoid receptors from the cytoplasm to the nucleus. Parionte and Miller (2001) suggest that this mechanism may provide one possible explanation for how treatment with antidepressants results in normalization of the HPA-axis hyperactivity in patients with depression.

While there was research focusing on HPA-axis dysregulation, there was another line of research evaluating dopamine (DA) activity in PMD versus NPMD. Previous studies have shown that CSF levels of a metabolite of DA, homovanillic acid (HVA), are low in patients with NPMD. (Sher et al., 2006; Reddy et al., 1992) However, Rothschild et al., (1987) showed that DA plasma levels are elevated in PMD, but not in NPMD. Others have shown that HVA is elevated in blood and CSF in PMD, but not in NPMD. (Sweeney et al., 1978; Aberg-Wistedt et al., 1985) The relationship between the findings of HPA-axis dysregulation and elevated DA in PMD was realized by Langlais et al., (1984; 1985) and others (Wolkowicz et al., 1986; Rothschild et al., 1984, 1987; Banki et al., 1983) who showed that glucocorticoids can increase DA in rat brain and human plasma and increase HVA in rat brain and human CSF. Based on these findings, Schatzberg and Rothschild hypothesized that psychotic symptoms in depression were secondary to the effects of hypercortisolemia on DA systems. (Schatzberg & Rothschild, 1992; Schatzberg et al., 1985) Maguire et al., (1987) showed a positive correlation between plasma free HVA and post dexamethasone log plasma cortisol levels ($r=0.59$; $p=0.02$).

7. Treatment strategies for PMD

The observations that DA activity is elevated in PMD have provided the rationale for the findings that antipsychotic medications significantly improve response rates when combined with antidepressant medications. Spiker et al., (1985) carried out one of the first randomized, double-blind prospective studies. Patients were randomized to amitriptyline monotherapy, perphenazine monotherapy, or combined amitriptyline plus perphenazine over a 5 week period; the response rates were 41% (7/17), 19% (3/16), and 78% (14/18) respectively. These results established the standard of practice of using combined antidepressant and antipsychotic medications for the treatment of PMD from that point forward. With the introduction of SSRIs, SNRIs, atypical antidepressants and atypical antipsychotic medications, there have been new treatment strategies using SSRI or SNRI monotherapy, atypical antipsychotic monotherapy, or atypical antipsychotic medications combined with an SSRI, or SNRI. In a series of 6-week treatment studies of PMD using SSRI or SNRI monotherapy, Gatti et al., (1996) and Zanardi et al., (1996;2000) showed high remission rates with fluvoxamine (84%), sertraline (72%), and venlafaxine (50%). In addition, Zanardi et al., (1997), in a 30 month, maintenance, open study of fluvoxamine remitters, found a relapse rate of only 20%. However, these studies lacked a control group and a validated instrument for the identification of psychosis. (Rothschild & Phillips, 1999) In addition, there has been no replication of these results. In an 8-week open study comparing the efficacy of sertraline monotherapy in PMD ($n=25$) versus NPMD ($n=25$), Simpson et al., (2003) found remission rates of 16% and 64% in patients with PMD and NPMD respectively ($p=.001$).

The atypical antipsychotics block both 5-HT₂ and DA receptors, which, theoretically, make them potential candidates for treating both depression and psychosis. There was a series of case reports and small open studies in the 1990's suggesting that atypical antipsychotic monotherapy was effective in treatment resistant PMD. (Ranyan and Meltzer, 1996; Dassa et

al., 1993; Lane and Chang 1998; Hillert et al., 199) To test the efficacy of atypical antipsychotic monotherapy, Muller-Siecheneder et al., (1998) compared the efficacy of risperidone monotherapy (n=16) versus the combination of haloperidol and amitriptyline (n=18) in the treatment of PMD. Both arms of the study showed improvement in depression and psychosis, but combined treatment was significantly better than monotherapy on scores for depression, BRMES, (p=.002) and psychosis, BPRS, (p=.016) More recent studies also support the value of combined atypical antipsychotic and antidepressant medications over atypical antipsychotic monotherapy. Rothschild et al., (2004) reported on two identical parallel trials where PMD patients were randomized to combined olanzapine/fluoxetine (OFC), olanzapine monotherapy (OLAN), or placebo (PLB); the HAM-D-24 response rates were 63.6%, 34.9%, and 28% respectively in Trial 1. Olanzapine/fluoxetine response rates were significantly higher than OLAN monotherapy (p=.027) and PLB (=0.004). There were no significant differences among the three arms in Trial 2. (Figure 5)

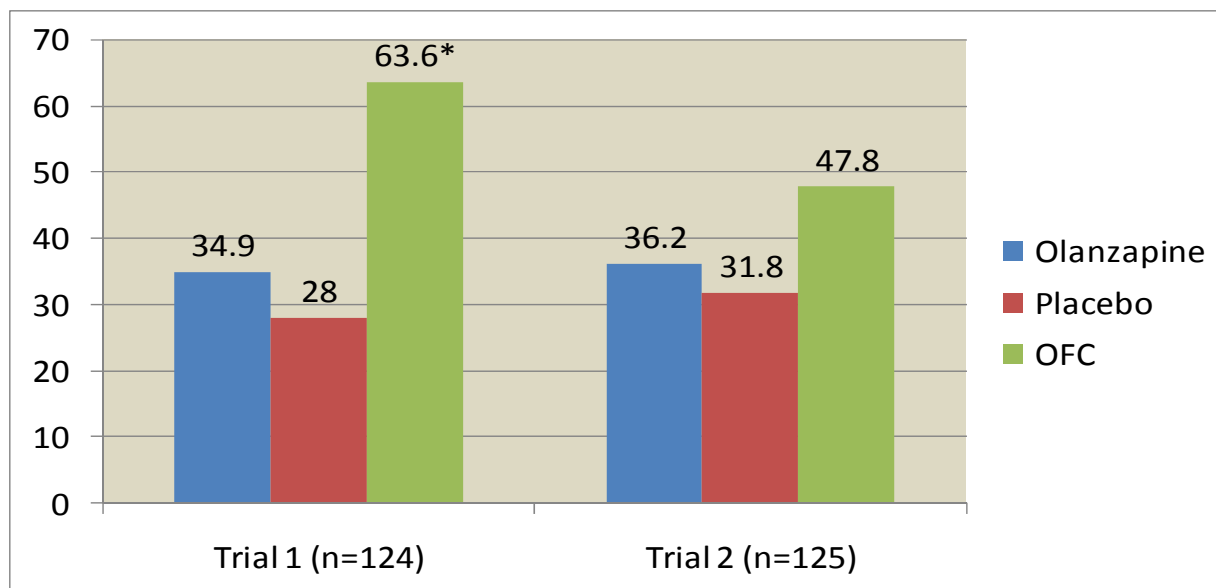


Fig. 5. (Rothschild et al., 2004; adapted) 8-Week Randomized Trial Olanzapine vs. OFC vs. PI (HAM-D-24 Response Rates - Trial: 1 OFC vs. Olan *p=.027; OFC vs. PI p=.004)

The only other randomized clinical trial comparing combined atypical antipsychotic/antidepressant with atypical antipsychotic monotherapy was the STOP-PD study, A National Institutes of Mental Health funded, multi-center study, reported by Meyers et al., (2009). (Figure 6)

In the STOP-PD study, patients were randomized to olanzapine plus sertraline (OLAN/SERT) (n=129) or olanzapine plus placebo (OLAN/PLB) (n=130) and treatment was continued for 12 weeks. The OLAN/SERT group remission rate separated from the remission rate for the OLAN/PLB group at week-8; the remission rate for OLAN/SERT continued to be significantly better than the remission rate for the OLAN/PLB group through week-12 (Hochberg α level of .05 from χ^2 analysis). Remission rates at last assessments were 41.9% and 23.9% for the OLAN/SERT and OLAN/PLB groups respectively. There is only one randomized controlled study comparing combined atypical antipsychotic and antidepressant medications with antidepressant monotherapy. Wijkstra et al., (2010a), in a 7-week trial, randomized patients to combined quetiapine plus venlafaxine

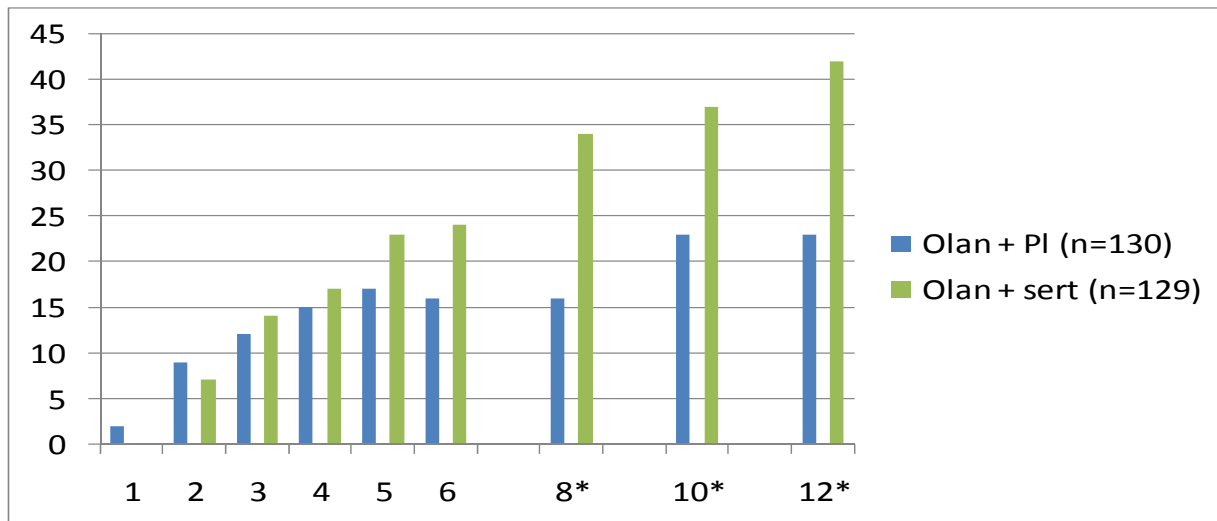


Fig. 6. (Meyer et al., 2009; adapted) STOP-PD: Remission for Olan + Sertraline vs. Olan + Placebo (* Hochberg α level of .05 from χ^2 analysis)

(QUET/VEN) (n=42), venlafaxine monotherapy (VEN) (n=39), or imipramine monotherapy (IMI) (n=41). There were no significant differences among the three groups with regards to remission rates. However, there was a significant difference with regards to HAM-D-17 response rates (response rate=50% reduction in HAM-D-17 from baseline and HAM-D-17 score at endpoint of ≤ 14) between QUET/VEN versus VEN (RD=32.5{95%CI:11.8; 53.2) at week-7. Based on these four randomized controlled studies, combined treatment with an atypical antipsychotic medication with an antidepressant is recommended. There have been no randomized controlled studies with the partial dopamine agonist, aripiprazole. In an open study, Matthews et al., (2009) published the first study combining aripiprazole with the SSRI, escitalopram. (Figure 7) Patients on this combination treatment showed remission rates of 42% by week-4 and 50% by week-7. Matthews et al., (2009) suggested that this rapid response may be due to the possibility that the SSRI, escitalopram, augmented the antipsychotic effect of aripiprazole through the established relationship of raphe nucleus serotonin inhibitory activity on ventral tegmental area dopamine cells and the possible augmentation of escitalopram by aripiprazole through 5HT2A blocking.

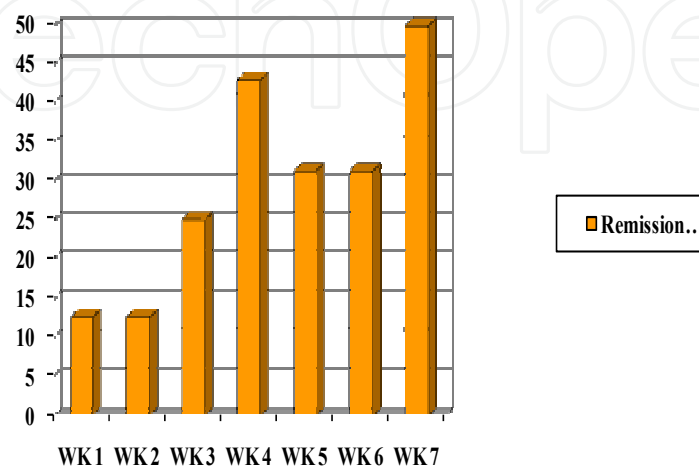


Fig. 7. (Matthews et al., 2009; adapted) PMD Remission Times: Aripiprazole/Escitalopram

Studies by Rothschild et al., (1999) and Kaiya et al., (1990) suggest that atypical antipsychotics are superior to typical antipsychotic medications for the treatment of PMD based on efficacy and time to response. Based on current findings, the ideal treatment for PMD might be the combination of an atypical antipsychotic with either an SSRI or SNRI; however, there needs to be a head-to-head trial comparing an SSRI or SNRI with a norepinephrine uptake blocker in combination with an atypical antipsychotic medication in order to validate this hypothesis. (Matthews, et al., 2009)

Recent research has used a novel approach for the treatment of PMD by targeting the HPA-axis hyperactivity associated with PMD. (Thakore & Dinan, 1995) There have been two strategies, inhibition of cortisol synthesis and blockade of the GR II receptors with antagonists. In a 4-week randomized, double blind, placebo controlled study of 20 medication-free NPMD patients, eight of whom had elevated cortisol levels, Wolkowitz et al., (1999) randomized patients to ketoconazole (400-800 mg/d) or placebo for 4 weeks. Ketoconazole was associated with improvements in depression ratings only in those patients with elevated cortisols. Forty-eight percent of ketoconazole treated hypercortisolemic patients showed a significant drop in HAM-D-21 compared to 6.6% of the placebo group ($p < .03$). In preclinical studies, mifepristone has been shown to be an antagonist at the GR II receptor. (de Kloet et al., 1998) This finding has led to a series of studies assessing the efficacy and safety of mifepristone (RU486) in the treatment of PMD. Early studies by Belanoff et al., (2001, 2002) and Simpson et al., (2003) (Figure 8) demonstrated improvement in both depression and psychosis in a dose dependent manner.

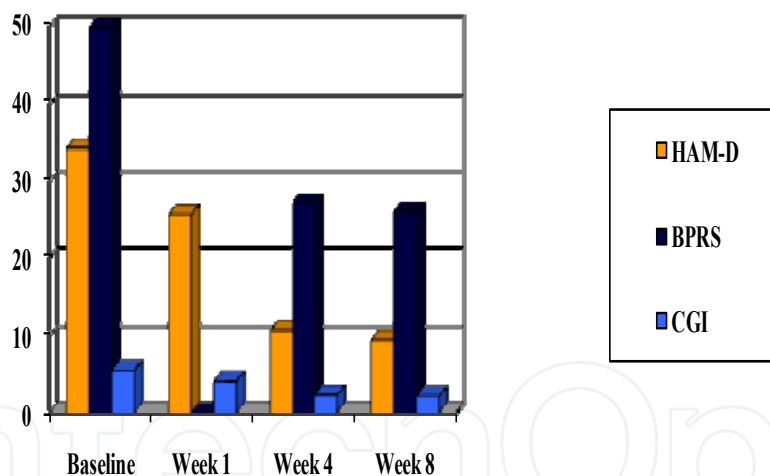


Fig. 8. (Simpson et al., 2005 adapted) Mifepristone: N=20; 6-week course; open-label; LOCF

However, more recent studies point to psychosis as the primary target of response. (DeBattista et al., 2006) Blasey et al., (2009), in a multi-site study (n=29), 56 day, placebo controlled study, demonstrated a rapid reduction in the Brief Psychiatric Rating Scale-Positive Symptoms Subscale (BPRS-PSS) in only 7 days with mifepristone compared to placebo; response rates were defined as a 50% reduction in BPRS-PSS from baseline at both days 7 and 56. BPRS-PSS response rate was determined by mifepristone plasma level. (Figure 9)

Patients with mifepristone plasma levels ≥ 1800 ng/ml were more likely to respond than patients on placebo; however, there were differences in responses between the original 20 research sites versus the 9 added research sites (Intent-to-treat: OR=2.4, $p = .03$; Initial sites: OR=4.1, $p = .002$).

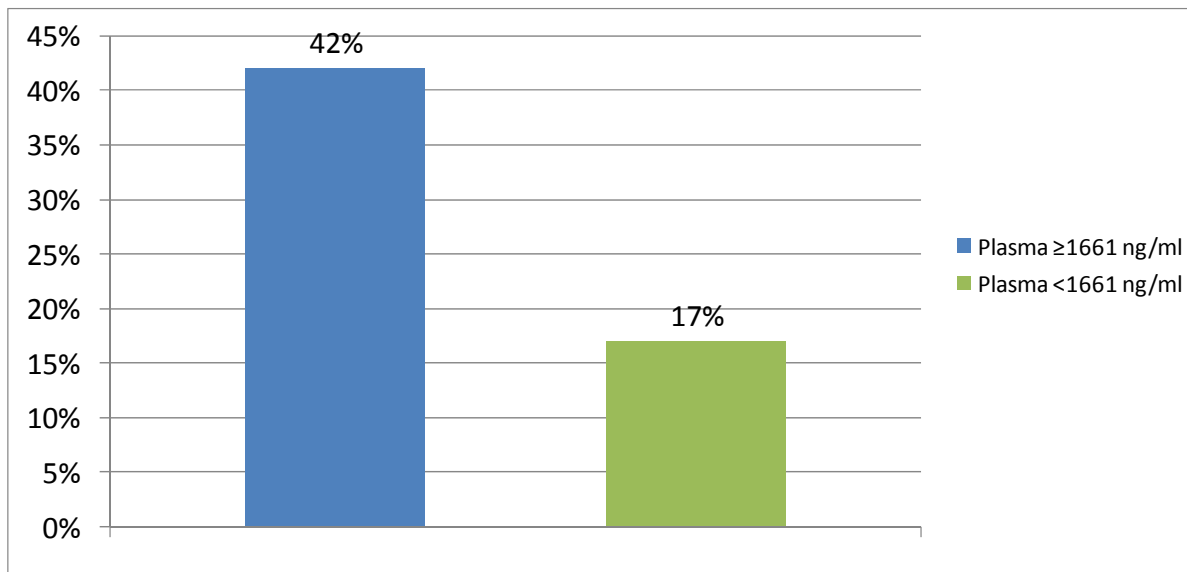


Fig. 9. (Blasey et al., 2009; adapted) Mifepristone: BPRS-PSS Response Rate at Days 7 and 56 (50% ↓ from Baseline; $p=.018$) (n=207)

Electroconvulsive therapy has been shown to be very effective in treating both neurovegetative symptoms of depression and psychosis. In an early review by Solan et al., (1988) they concluded that ECT response rates in PMD were not significantly different than the response rates in NPMD. However, two more recent studies have shown that the presence of psychosis is a predictor of ECT response in major depressive disorder. Petrides et al., (2001) found that complete remission rates for PMD (n=77) versus NPMD (n=176) were 95% and 83% respectively. Figure 10)

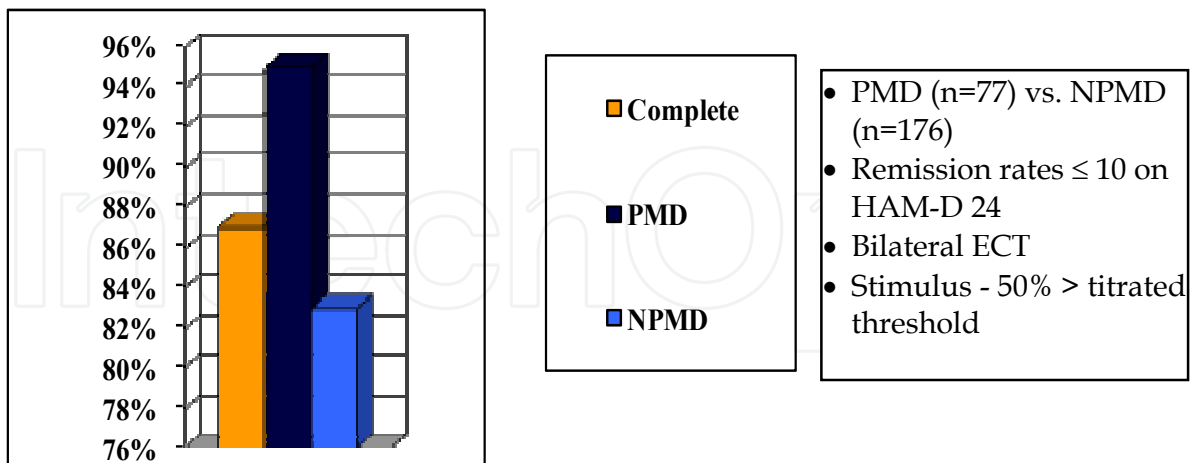


Fig. 10. (Petrides et al., 2001,adapted) ECT Remission Rates in Psychotic vs. Nonpsychotic MDD

In an European study, Birkenhager et al., (2003) found response rates of 92% and 55% in delusional depression versus non delusional depression respectively; remission rates were 57% and 24% respectively. (Figure 11)

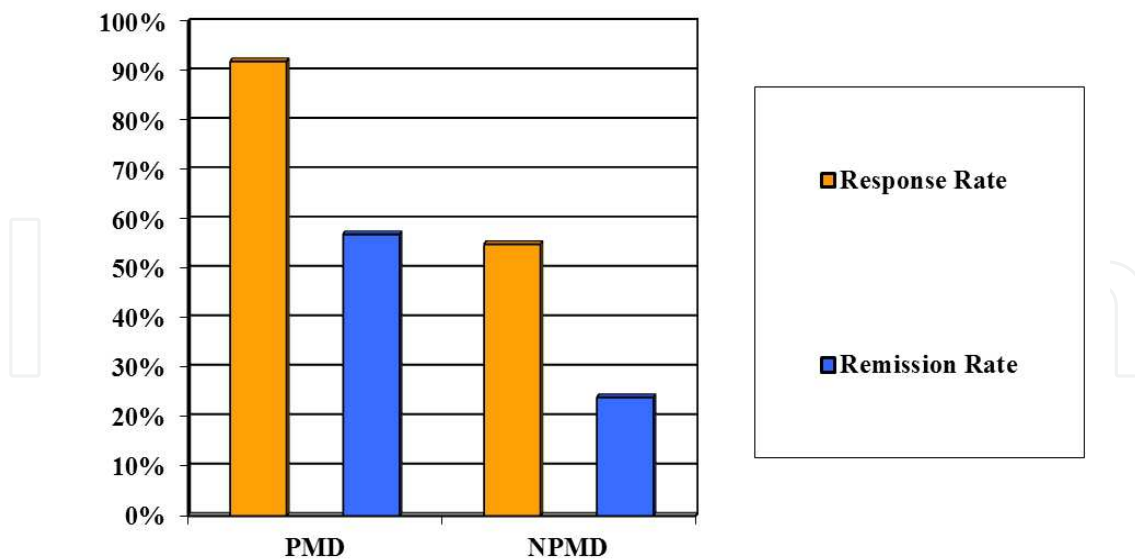


Fig. 11. (Birkenhager et al., 2003; adapted) ECT Response in Delusional vs. Non-delusional Depressed Inpatients

There is no evidence that psychotherapy alone is effective in the treatment of PMD as is the case for mild to moderate NPMD outpatients. (Rush et al., 1977) Gaudiano and Herbert (2006) combined Acceptance and Commitment Therapy (ACT) to enhanced treatment as usual (ETAU) (n=19) versus ETAU (n=21) in an inpatient populations of PMD. Acceptance and Commitment Therapy focuses on acceptance of one's distress rather than ruminating about contributing factors from the past and/or worries about future negative predictions, both of which are out of one's absolute control. Acceptance allows one to observe one's distress as an opportunity to learn and thus improve problem solving. Acceptance also enables one to proceed with achieving value-based goals; thus, with acceptance, value-based goals can be achieved in spite of one's distress. Gaudiano and Herbert taught patients to accept their psychotic symptoms without judgment and to proceed with achieving their value-based goals. For their primary outcome measure, they found that 44% of ACT+ETAU versus 0% of ETAU had a ≥ 2 standard deviation improvement at discharge from baseline on total BPRS ($\chi^2=5.14$, $p<.05$). In addition, there were no significant differences in change scores from baseline to discharge between the two groups on the BPRS-PSS subscale, but the percent change scores on the BPRS mood subscale from baseline to discharge for ACT+ETAU versus ETAU were 70% and 30% respectively ($\chi^2=3.60$, $p=.058$).

8. Longitudinal course of PMD

Patients with PMD have a more severe course to their illness compared to patients with NPMD. At one year follow-up, patients with PMD were more likely to be in an episode, had significantly higher numbers of episodes, and psychiatric hospitalizations. (Robinson and Spiker, 1985) Data from the Epidemiology Catchment Area (ECA) study found that patients with PMD, compared with NPMD, have significantly greater impairment in functioning as measured by percent on public assistance (17.5% of PMD; 7.2% of NPMD) and on disability (15.9% of PMD; 6.7% of NPMD). (Johnson et al., 1991) As with schizophrenia and bipolar

disorder, PMD is associated with higher rates of morbidity and mortality from medical conditions. Vythilingam et al., (2003) found that the mortality rate was two-fold higher for PMD versus NPMD and that 88% of the deaths were due to medical disorders.

In a 10-year prospective study, Coryell, et al., (1996) found that patients with PMD spent more weeks in full major depressive disorder than patients with NPMD. (Figure 12)

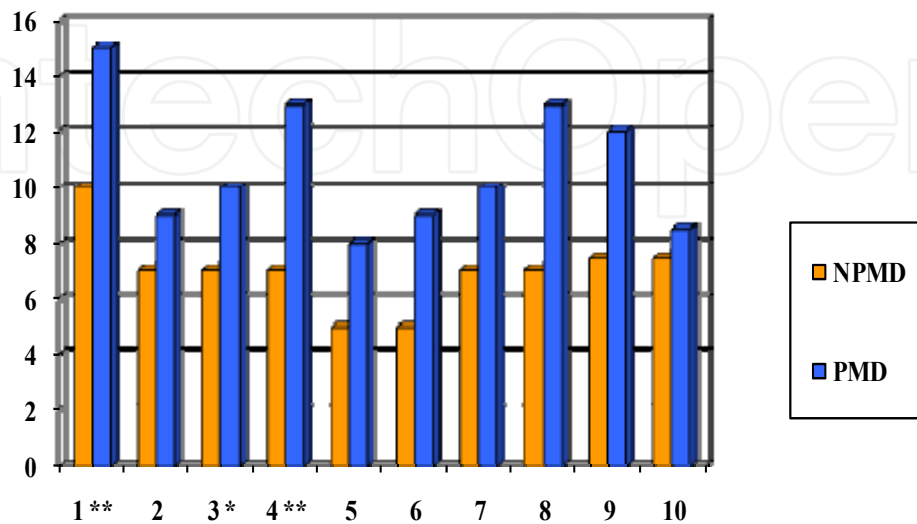


Fig. 12. (Coryell et al., 1996; adapted) Number of Weeks in Full Major Depression (10 YEARS) (* $p < .05$; ** $p < .01$)

They also found that the recovery period was significantly prolonged with PMD versus NPMD. The percents of patients who had not recovered from their index episodes of PMD versus NPMD were 36.4% versus 28.2% at year-1 ($p < .05$), 19.7% versus 7.8% at year- 5 ($p < .001$), and 14.3% versus 4.6% at year-10 ($p < .001$) respectively. However, when compared to schizophrenia, Tsuang and Coryell, (1992) showed that recovery rates from index psychotic episodes were significantly better for PMD versus schizophrenia: 54% versus 4% at year-1, 75% versus 18% at year- 5; and 75% versus 21% at year-8 respectively (Wilcoxon $\chi^2=15.4$, $df=1$, $p < .0001$). Wijkstra et al., (2010b) showed that remission rates continue to improve by 27.5% over a 4-month continuation of the same medications that resulted in meeting criteria for response at week-7. Thus, for patients who have responded partially, but have not achieved remission, continuation of treatment for another few months may provide added benefit.

As noted above, PMD is a highly relapsing disorder. Aaronson et al., (1988) reported on a 3-year retrospective study of 52 PMD inpatients who had achieved remission by discharge. Forty-five of the 52 patients (86%) relapsed over the 3-year period following discharge. There were 98 episodes of relapse among the 45 patients who relapsed. Eight-two (82.5%) of the 98 episodes occurred within the first year after discharge from inpatient treatment. Seventy-one (86%) of the first year relapses occurred with patients on no antipsychotic medications or tapering doses of antipsychotic medications. Twenty-nine (41%) of the 71 relapses associated with antipsychotic medications changes occurred despite stable doses of antidepressants. The relapse rate for patients on stable doses of antidepressant and antipsychotic medications during year-1 was 13.4%. In addition, 42% of the first year relapses occurred in the first 3-month period of discontinuation or decrease in dose of antipsychotic medications. Aronson et al., (1988) concluded that combined treatment with

antipsychotic and antidepressant medications beyond the first year of recovery is recommended. Coryell, et al., (1996) reported on the percent of PMD patients on antidepressant and antipsychotic medications at the time of first relapse after achieving remission. They found 48 % were on antidepressant but only 20% were on antipsychotic medications.

There have been few accessible guidelines available for clinicians to use in deciding maintenance treatment of PMD. In a survey of 304 practicing clinicians, who were attending a psychopharmacology course sponsored by the Department of Psychiatry at Massachusetts General Hospital in 2001, Matthews, (2001) queried clinicians as to whether they continued their PMD patients on antidepressant and antipsychotic medications beyond 12 months after they achieved remission. Fifty-six percent of the clinicians indicated that they continued antidepressant medications beyond 12 months, whereas, only 16% reported that they continued antipsychotic medications beyond 12 months. Rothschild and Duval, (2003) provided potential guidelines for clinical decision making regarding maintenance treatment for PMD. They reported on 40 patients diagnosed with PMD who had achieved remission after 5 weeks of acute treatment with the combination of perphenazine plus fluoxetine. These patients were continued on the combination treatment for an additional 4 months; at the end of the 4-month continuation phase, they were tapered off perphenazine and continued on fluoxetine monotherapy for an additional 8 months of maintenance treatment. There were no relapses during the 4-month continuation phase; however, 8 (27%) of the 30 patients who continued into the maintenance phase relapsed. Rothschild and Duval reported that the predictors of relapse included a longer index episode, a history of more frequent episodes, an earlier age of onset of PMD, and less than 30 years of age at index episode. In the recent STOP-PD study, Andreescu et al., (2007) reported on the adequacy of pharmacological treatment on the first 100 patients at study entry. The rates of adequate or high doses of antidepressants, antipsychotics, and combined antidepressant/antipsychotic medications were 48%, 6%, and 5% respectively.

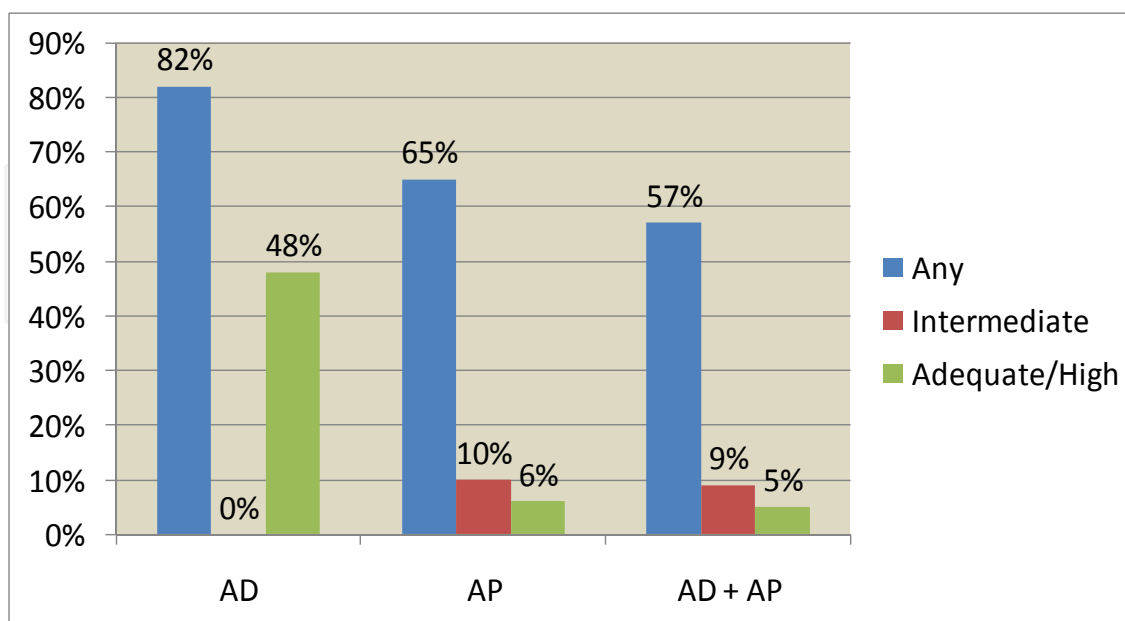


Fig. 13. (Andreescu et al., 2007; adapted) STOP-PD: Adequate Pharmacological Treatment on Study Entry (n=100)

(Figure 13) Interestingly, these findings are comparable with results reported by Mulsant et al. (1997), who found that only 4% (2/53) of PMD patients referred for ECT received an adequate medication trial, whereas 52% (70/134) of NPMD patients received an adequate medication trial. In addition, 47% (25/53) of PMD received either no antipsychotic medication or the duration of treatment with an antipsychotic medication was for less than three weeks. Only 15% received antipsychotic doses greater than 200 mg daily of chlorpromazine equivalents. Thus, it appears that prescribing practices for PMD had not changed significantly for the 10-year period from 1997 to 2007. (Figure 14) Unfortunately, there have been very few acute and long-term clinical trials for the treatment of PMD compared with NPMD, bipolar disorder, or schizophrenia; thus, there is minimal data available to serve as a guideline for practicing clinicians.

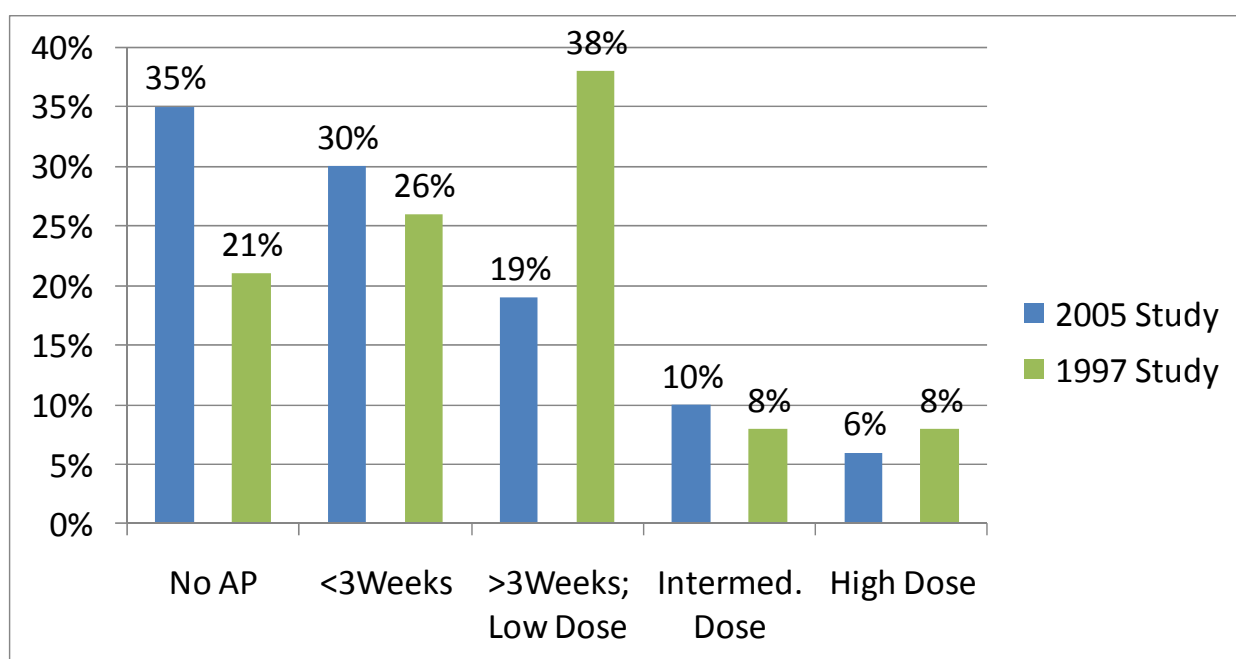


Fig. 14. (Andreescu et al., 2007; adapted) STOP-PD: % Receiving Adequate Antipsychotics at Study Entry in 2005 vs. 1997

9. Conclusions

Combined antidepressant and antipsychotic treatment continues to be the standard for acute and maintenance treatment of PMD. Selective Serotonin Reuptake Inhibitor monotherapy may be effective in treating PMD during the acute, continuation, and maintenance phases; however, there advantage may be in helping to augment atypical antipsychotic medications in treating psychotic symptoms, but further studies are required. Atypical antipsychotics in combination with SSRIs may increase the response rate and decrease the time to response. SSRIs may augment atypical antipsychotics by inhibiting DA cells and atypical antipsychotics may augment SSRIs by blocking 5HT_{2A} receptors; however, studies are needed to support these hypotheses. Preliminary data suggests mifepristone, a glucocorticoid receptor antagonist, treats psychotic symptoms in PMD rapidly and the response has durability beyond discontinuation of the drug after only 7 days of treatment. Psychotic features in major depressive disorder predict response to ECT.

Psychotic major depression is a highly relapsing illness with a long recovery period, therefore, long-term prophylactic treatment with combined antidepressant and an antipsychotic medications is recommended.

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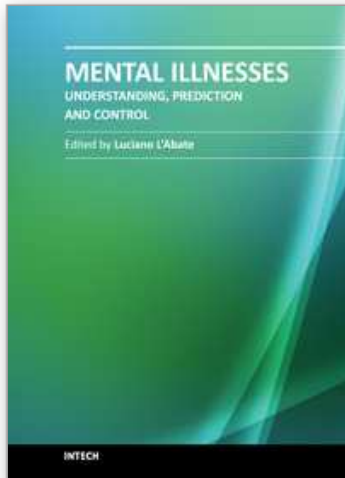
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In the book "Mental Illnesses - Understanding, Prediction and Control" attention is devoted to the many background factors that are present in understanding public attitudes, immigration, stigma, and competencies surrounding mental illness. Various etiological and pathogenic factors, starting with adhesion molecules at one level and ending with abuse and maltreatment in childhood and youth at another level that are related to mental illness, include personality disorders that sit between mental health and illness. If we really understand the nature of mental illness then we should be able to not only predict but perhaps even to control it irrespective of the type of mental illness in question but also the degree of severity of the illness in order to allow us to predict their long-term outcome and begin to reduce its influence and costs to society. How can we integrate theory, research evidence, and specific ways to deal with mental illness? An attempt will be made in the last conclusive chapter of this volume.

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