Differential Response to Combined Treatment in Patients With Psychotic Versus Nonpsychotic Major Depression

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Abstract: Research has demonstrated that depressed patients with psychotic features show poorer outcomes when treated with pharmacotherapy alone compared with those without psychotic features. However, research has not investigated whether this differential response also applies to combined treatment that includes pharmacotherapy and psychotherapy. In the current study, data were pooled from two clinical trials in which patients diagnosed with major depressive disorder with or without psychotic features were treated with combined treatment. Although similar in severity at pretreatment, results indicated that patients with psychotic depression showed a poorer response in terms of depression severity at postoutpatient treatment and at 6-month follow-up compared with those with nonpsychotic depression. Following treatment, patients with psychotic depression were over four times as likely to exhibit high levels of depression and suicidal ideation. Current state-of-the-art combined treatments have poorer efficacy in depressed patients with psychotic symptoms, and adapted treatment approaches are needed.

Key Words: Depression, psychosis, combined treatment, randomized controlled trial, suicidal ideation.

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Major depression with psychotic features represents a severe mood disorder diagnosed when a patient exhibits hallucinations and/or delusions in the context of a depressive episode (American Psychiatric Association, 2000). Psychotic depression (PD) is estimated to be present in up to 25% of consecutively depressed patients admitted to the hospital (Coryell et al., 1984). Relapse rates in this group are 50% to 92% within 2 to 14 months after the initial episode (Aronson et al., 1988). However, psychotic features in depressed patients often go overlooked because clinicians fail to adequately assess for these symptoms, and some patients may underreport due to paranoia (Lykouras et al., 1986). Compared with nonpsychotic depression (NPD), patients with PD are characterized by greater depression severity, suicidality, psychomotor disturbances, anxiety, cognitive impairments, hypothalamic/pituitary/adrenal axis activity, cluster A personality features, interpersonal problems, and family history of depression and psychosis (see Schatzberg, 2003 for a review). Differences between psychotic and nonpsychotic depressed patients have led some to argue that PD should be classified as a distinct diagnostic entity based on the number of biological and behavioral symptoms specific to the disorder (Schatzberg and Rothschild, 1992).

In addition to exhibiting greater symptom severity, PD patients are difficult to treat and typically inadequately treated. They show a poorer response to antidepressants compared with NPD patients (Brown et al., 1982) and typically require adjunctive treatment with antipsychotic medications (Vega et al., 2000). Although combined pharmacotherapy and psychotherapy produce improvements in efficacy when treating NPD patients (Friedman et al., 2004), particularly for more severely depressed patients, little evidence is available on psychotherapy or combined treatment response in PD (Bishop et al., 1986). PD patients traditionally are excluded from depression trials. However, various psychosocial treatments have been shown to positively impact the core symptoms of psychotic disorders when added to pharmacotherapy (Mueser et al., 2002).

Representing the first such study to our knowledge, we compared treatment response in PD and NPD patients who received combined pharmacotherapy plus an efficacious psychotherapy for depression (behavior therapy, cognitive therapy, or family therapy). However, the psychotherapies provided were not adapted specifically for patients with psychotic depression. Therefore, we hypothesized that PD patients would show poorer outcomes compared with NPD patients, even when provided traditional but state-of-the-art combined treatment of depression.

METHODS

Data were pooled from two randomized controlled trials for depression that had very similar methodologies. Please refer to the original studies for more detailed descriptions. In study 1, inpatients with major depressive disorder (MDD) were randomly assigned to pharmacotherapy (PT), PT plus cognitive therapy (CT), or PT plus social skills training, which began during hospitalization and continued through outpatient treatment (Miller et al., 1989; Miller et al., 1988). In study 2, hospitalized (inpatient or day hospital) patients with MDD were randomly assigned to PT, PT plus CT, PT plus family therapy (FT), or PT plus CT and FT, which began shortly after discharge from the hospital (Miller et al., In press). Additionally, in study 2, patients were matched or mismatched to treatments based on relevant pretreatment variables. Average length of inpatient stay was 26 days in study 1 and 14 days in study 2. Although a detailed description of results is beyond the scope of this paper, both trials showed the superiority of combined treatment compared with PT alone, and response rates were similar across studies. In general, one form of psychotherapy used in the trials was not superior to another, but study 2 found some evidence for a matching effect. PT in both studies included semistructured administration of antidepressants prescribed at standard doses. Psychotherapy provided in both studies was manualized and delivered by expert clinicians. PD patients in both studies were

treated with adjunctive antipsychotic medications as appropriate. Chart review confirmed that 90% of PD patients were prescribed antipsychotics during outpatient therapy.

Both studies had similar inclusion criteria: primary MDD diagnosis, English-speaking, age 18 to 65, and admission scores >17 on the Modified Hamilton Rating Scale for Depression (MHRSD; Miller et al., 1985) and on the Beck Depression Inventory (Beck et al., 1961). Exclusion criteria included significant cognitive impairment; diagnoses of bipolar disorder, alcohol/drug dependence, or schizophrenia; electroconvulsive therapy; or contraindications for antidepressant use. Diagnoses were based on the Diagnostic Interview Schedule (Robins et al., 1981) for study 1 and the Structured Clinical Interview of DSM-III-R (Spitzer et al., 1990) for study 2 conducted during hospitalization by trained assessors. Outpatient treatment lasted 20 to 24 weeks. Blind raters assessed patients using the 17-item MHRSD and the Modified Suicidal Ideation Scale (MSSI; Miller et al., 1986) at hospital admission, discharge, postoutpatient treatment, and 6-month follow-up. In study 1, the Symptom Checklist-90 (SCL-90; Derogatis et al., 1973) also was administered at each time point.

A repeated-measures analysis of variance (ANOVAs) was conducted on MHRSD scores between groups (PD versus NPD) for the inpatient treatment phase to examine any admission or discharge group differences, as well as to assess change over time. An analysis of covariance covarying discharge (preoutpatient treatment) scores was conducted on the outpatient phase (postoutpatient treatment through follow-up) to assess treatment-related changes. The Cohen *d* was computed to describe the magnitude of treatment effects, with .2, .5, and .8 representing a small, medium, and large effect, respectively (Cohen, 1988). High symptom severity following treatment was designated by MHRSD scores >14, representing "in episode" status (Frank et al., 1991), and MSSI scores >20, representing high levels of suicidal ideation (Miller et al., 1986). These two criteria were combined as they did not completely overlap and provided a more clinically significant and reliable indicator of high severity. Group severity rates were compared by computing χ^2 tests and calculating odds ratios. All analyses were based on two-tailed tests and were intent-to-treat to provide the most conservative estimate of treatment response. Analyses were limited to those receiving combined treatment, as the sample size of PD patients who received PT alone in the studies was small ($N = 5$). MSSI scores were not analyzed using parametric tests due to excessive skewness in the data that was not correctable by score transformations.

RESULTS

Severity of illness in the current sample was similar to that reported in pharmacotherapy trials of PD (e.g., Rothschild et al., 2004). In study 1 (Miller et al., 1988), repeated-measures ANOVAs showed significant group main effects, with PD patients having higher levels of psychotic symptoms ($F_{1, 70} = 67.89$; $p < 0.05$) and paranoia ($F_{1, 64} = 94.56$; $p < 0.01$) as assessed by the SCL-90 over the course of the study compared with NPD patients. Although SCL-90 data were not available for patients in study 2 (Miller et al., In press), chart reviews confirmed that 73% were experiencing hallucinations, 60% were experiencing delusions, and 40% were experiencing both types of symptoms over the course of the study. Based on independent-samples *t* tests, no significant differences were found between the two studies in patient age (study 1 $M = 35$; study 2 $M = 37$; p = NS) or MHRSD admission scores (study 1 $M = 23.8$; study 2 $M = 24.0$; p = NS). Furthermore, a χ^2 test showed no significant gender differences (study 1 females = 69%; study 2 females = 65%; p = NS). Therefore, results indicated that PD patients were indeed experiencing psychotic symptoms throughout the study and that it was acceptable to combine the samples from the two studies in subsequent analyses.

Table 1 shows the means and *SD*s for study variables by diagnostic group. In the combined sample of patients from studies 1 and 2, no significant differences were found between PD ($N = 14$) and NPD ($N = 105$) patients on age or gender variables (p values = NS). Based on a χ^2 analysis, the proportion of PD (37%) and NPD (41%) patients with high levels of suicidal ideation (MSSI > 20) at hospital admission was not significantly different (p = NS). In addition, rates of dropout (PD = 14%; NPD = 15%) and missing follow-up data (PD = 21%; NPD = 28%) did not differ between groups (p values = NS). In general, PD and NPD patients showed similarly high levels of severity at hospital admission.

First, we examined the inpatient phase of treatment to test for admission or discharge group differences. A two (PD versus NPD) by two (admission and discharge) repeated-measures ANOVA on MHRSD scores showed a significant time main effect ($F_{1, 117} = 103.63$; $p < 0.001$), but no group main effect or interaction (p values = NS). Results indicated large symptom reductions over the course of hospitalization regardless of group status ($d = 1.81$).

Next, we conducted analyses on the outpatient treatment phase. A two (PD versus NPD) by two (postoutpatient and follow-up) repeated-measures analysis of covariance covarying discharge (i.e., preoutpatient treatment) scores showed only a significant group main effect ($F_{1, 116} = 14.19$; $p < 0.05$). Tukey post hoc tests indicated that PD patients had significantly higher MHRSD scores compared with NPD patients at postoutpatient and at 6-month follow-up (p values < 0.05). Effect size differences between groups were in the medium range at postoutpatient ($d = .46$) and at follow-up ($d = .51$). Results indicated that NPD patients improved more following outpatient treatment than PD patients (Fig. 1).

Finally, we examined the percentage of PD and NPD patients who continued to show high levels of depression and

TABLE 1. Characteristics and Combined Treatment Response for Depressed Patients With or Without Psychotic Features[a]

Variable	Psychotic % (*N*)	Nonpsychotic % (*N*)	Significance test
Sample	12 (14)	88 (105)	
Gender			χ^2 = NS
Women	71 (10)	73 (76)	
Men	29 (4)	27 (29)	
Dropout			
Postoutpatient	14 (2)	15 (16)	χ^2 = NS
Follow-up	21 (3)	28 (29)	χ^2 = NS
High symptom severity			
Postoutpatient	29 (4)	9 (9)	$\chi^2(1) = 5.08$; $p < 0.05$
Follow-up	21 (3)	7 (7)	$\chi^2(1) = 3.50$; $p = 0.06$
	***M* (SD)**	***M* (SD)**	
Age	36.3 (10.3)	36.7 (12.0)	t = NS
MHRSD			
Inpatient phase			Group effect: F = NS
Admission	25.1 (4.3)	23.8 (4.7)	
Discharge	14.0 (8.4)	12.8 (7.3)	
Outpatient phase			Group effect: $F(1,116) = 4.45$; $p < 0.05$
Postoutpatient	13.4 (10.2)	9.2 (7.8)	$p < 0.05$
Follow-up	14.0 (11.8)	8.9 (7.7)	$p < 0.05$

[a]High symptom severity = MHRSD > 14 and MSSI > 20.

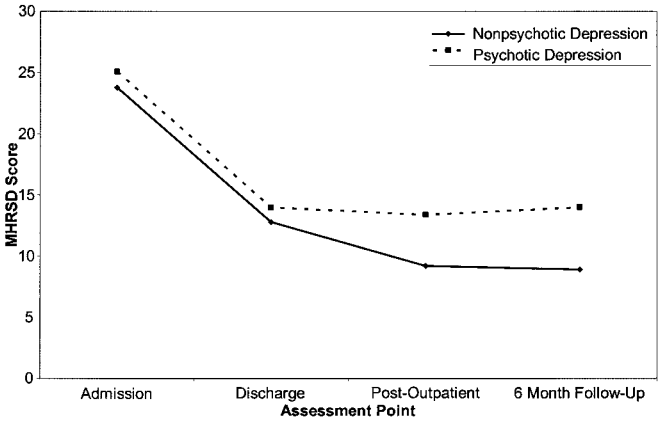

FIGURE 1. Combined treatment response in depressed patients with or without psychotic features.

suicidal ideation following treatment. Based on χ^2 analyses, significantly more PD compared with NPD patients met the high severity criteria at postoutpatient ($p < 0.05$). A marginally significant effect was found at 6-month follow-up ($p = 0.06$). The odds ratios were 4.26 (CI_{95} = 1.11–16.39) at postoutpatient and 3.82 at follow-up (CI_{95} = .86–16.92). In other words, the PD group was 4.26 times more likely to exhibit high symptom severity at postoutpatient compared with the NPD group, and 3.82 times more likely at follow-up.[1]

DISCUSSION

In the current study, results of treatment response in PD patients receiving combined pharmacotherapy plus psychotherapy were similar to those found in trials of PD patients treated with pharmacotherapy alone. Individuals with PD showed greater depression severity at postoutpatient treatment and at 6-month follow-up compared with patients with NPD. At postoutpatient, 29% of PD patients compared with only 9% of NPD patients showed high levels of depression and suicidal ideation. The risk of suicide in psychotic disorders is high as with mood disorders, and the combination of these two types of problems may put PD patients at particularly high risk (Warman et al., 2004).

Limitations of the current study included the small sample size, incomplete longitudinal data on psychotic symptoms and antipsychotic regimens, and the combination of different forms of psychotherapy. However, examination of available data did not support the role of several likely confounds, as PD patients had higher levels of psychotic symptoms consistent with their diagnosis, were treated with adjunctive antipsychotic medications when appropriate, did not exhibit differential dropout rates, and did not possess greater initial severity. Furthermore, research does not suggest that the various types of psychotherapy provided to patients in the two studies would be differentially efficacious (Beutler et al., 2000).

The sample size was too small to compare PD and NPD patients who received pharmacotherapy alone, although visual inspection of the data revealed a pattern similar to that found in the combined treatment sample. Nevertheless, it remains unclear whether PD patients receiving combined treatment improved more than similar patients receiving pharmacotherapy alone. Finally, it is important to note that although other studies have found higher depression severity in PD compared with NPD patients, these studies typically involved outpatient samples. The current sample comprised hospitalized patients with generally high levels of severity that did not differ significantly between groups at admission. Both groups improved considerably but similarly during the inpatient phase of treatment, with group differences emerging during outpatient treatment.

Recently, several randomized controlled trials have demonstrated the efficacy of cognitive behavior therapy (CBT) adapted to treat acute and residual psychotic symptoms (Gaudiano, 2005). We are not aware of any randomized controlled trials that have examined CBT for psychosis in patients with PD specifically. However, some studies have shown positive effects with mixed psychotic disorder samples that included such patients (Gaudiano and Herbert, In press). The potential benefits of CBT adapted for PD are promising but require further investigation at this point. Overall, results of the current study support the need to adapt current state-of-the-art psychosocial treatments for PD patients, especially due to the continued high levels of depression and suicidality found in this population after treatment.

[1]A similar pattern of results was found when examining only those high (>20) on the MSSI (e.g., postoutpatient: PD = 24%; NPD = 12%; $\chi^2 = 2.64$; $p = 0.10$). However, as some patients scored high on the MSSI but not on the MHRSD, we believed that criteria requiring high scores on both measures represented a more reliable assessment of severity.

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