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Challenges in the Treatment of Major Depressive Disorder With Psychotic Features

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Psychotic depression is associated with significant morbidity and mortality but is underdiagnosed and undertreated. In recent years, there have been several studies that have increased our knowledge regarding the optimal treatment of patients with psychotic depression. The combination of an antidepressant and antipsychotic is significantly more effective than either antidepressant monotherapy or antipsychotic monotherapy for the acute treatment of psychotic depression. Most treatment guidelines recommend either the combination of an antidepressant with an antipsychotic or ECT for the treatment of an acute episode of unipolar psychotic depression. The optimal maintenance treatment after a person responds to either the antidepressant/antipsychotic combination or the ECT is unclear particularly as it pertains to length of time the patient needs to take the antipsychotic medication. Little is known regarding the optimal treatment of a patient with bipolar disorder who has an episode of psychotic depression or the clinical characteristics of responders to medication treatments vs ECT treatments.

Key words: major depression with psychotic features/psychotic depression/delusional depression

Introduction

Psychotic depression or major depressive disorder with psychotic features is a serious illness during which a person suffers from the combination of depressed mood and psychosis, with the psychosis commonly manifesting itself as nihilistic type delusions, with the belief that bad things are about to happen. Unfortunately, until recently, the treatment of psychotic depression has not been studied to the same extent as other psychiatric disorders with similar prevalence[1] and remains an underdiagnosed[2] and undertreated[3] psychiatric disorder.

There has been a long-standing discussion as to whether psychotic depression is a distinct syndrome or simply represents a severe form of depression. Much of the debate stems from the fact that in *DSM-II*, published in 1968, "psychosis" meant severe and did not mean being out of touch with reality or having delusions or hallucinations. In 1970, Gerald Klerman and Eugene Paykel published an influential article that stated that in depression, there was a smooth continuum from mild outpatient depression to severe depression requiring inpatient hospitalization without any demarcation points.[4] Observations that psychotic depressed patients differed from nonpsychotic patients in their response to pharmacological treatments[5] led investigators to focus on more clearly defining this distinct clinical entity.

In 1992, as Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV was being planned, a strong argument was made in the *American Journal of Psychiatry* that there was sufficient evidence at that time from studies of clinical characteristics and symptoms, biology, family history, course and outcome, and treatment that psychotic depression should be a distinct illness in DSM-IV, separate from major depression.[6] *The American Journal of Psychiatry* article led to a position paper submitted to the DSM-IV Work Group on mood disorders.[7] The DSM-IV Work Group on mood disorders agreed[7] that the clinical relevance of specifically designating patients with psychotic depression was high and considered 2 options: (1) to continue the classification as in DSM-IIIR designating psychosis as decimal point under the severity code and (2) to designate psychotic depression as a separate syndrome "major depression with psychotic features." After much deliberation, the work group recommended the first option although it recognized it was less than optimal.[7] Thus, in DSM-IV[8] and DSM-IV text revision,[9] psychotic depression remained as a subclassification of major depressive dsorder.

Similarly, in the International Classification of Diseases, 10th revision (ICD-10), psychotic depression is

classified as a subtype of severe depression.[10] Arguments that psychotic depression meets the criteria for a valid psychiatric syndrome due to its distinct clinical presentation, neurobiology, heritability, prognosis, and treatment response continue to be made with the hope that this will change in ICD-11.[11]

In DSM-V, psychotic depression will remain as a subclassification of major depressive disorder. However, in DSM-V, psychotic features will be separated from the severity rating, and major depressive disorder with psychotic features will not necessarily need to be classified as "severe." This is a change from DSM-IV. Moreover, in DSM-V, a hierarchy giving precedence to mood-incongruent features is being introduced to allow classification of cases in which mood-congruent and mood-incongruent psychotic features coexist. After reviewing the epidemiology of psychotic depression and its distinction from schizophrenia and relationship to bipolar disorder, I will discuss the acute and long-term treatment of psychotic depression including several key questions such as should antidepressants and antipsychotics be combined for the treatment of psychotic depression? If combination therapy is used, what are the risks of side effects? What are the recommendations for maintenance treatment and relapse prevention?

Epidemiological Studies

Epidemiological studies of the prevalence of psychotic depression in the community indicate that it afflicts approximately 4 per 1 000 people in the general population although the community rates in people over the age of 60 have been reported to be between 14 and 30 per 1 000.[12,13] In a study of 18 980 people aged 15–100 years who were representative of the general populations of several European countries, the prevalence of psychotic depression was 4 per 1 000 people.[14]

In samples of patients with major depression, the rates of psychotic depression are considerably higher. In a European study of patients who met criteria for major depression, 18.5% of them also fulfilled criteria for major depressive episode with psychotic features.[14] In the United States, in the Epidemiologic Catchment Area Study,[15] 14.7% of patients who met criteria for major depression had a history of psychotic features.

In studies of patients with major depression in an inpatient setting, the prevalence rate of psychotic depression is even higher. In a study of consecutively admitted patients hospitalized for major depression, Coryell and colleagues[16] reported that 25% of the patients met criteria for psychotic depression. In samples of older inpatients with major depression, the prevalence of psychotic depression increases dramatically. Studies have found that the frequency of psychotic depression in people over age 60 in inpatient settings varies between 24% and 53%.[17]

Relationship of Psychotic Depression to Bipolar Disorder

Whether there is a relationship between psychotic depression and bipolar disorder has intrigued investigators for many years. Several studies have demonstrated that patients with psychotic depression, particularly those with an early age of onset, may have a higher risk than nonpsychotic depressed patients of subsequently developing bipolar disorder.[18–21] In addition, relatives of patients with psychotic depression have a higher prevalence of bipolar disorder compared with the relatives of patients with nonpsychotic depression,[22–24] and depressed relatives of patients with bipolar disorder are more likely to suffer from the psychotic subtype compared with depressed relatives of healthy controls.[25] A parental history of bipolar disorder has been shown to be a risk factor for psychotic depression but not for nonpsychotic depression.[26]

Missed Diagnosis of Psychotic Depression

Data from the National Institute of Mental Health (NIMH) Study of the Pharmacotherapy of Psychotic Depression (STOP-PD)[2] indicates that clinicians frequently miss the diagnosis of psychotic depression, in large part, due to a lack of recognition of the psychotic features. In the STOP-PD Study, 27% of 130 diagnoses among a well-characterized sample of patients with a research diagnosis of psychotic depression were initially incorrectly diagnosed. It is likely that the missed diagnosis rate observed in this study was a conservative estimate of the rate in the general clinical population because patients with comorbid conditions such as a history of substance abuse in the past 3 months or unstable medical conditions were excluded. Psychotic depression was most commonly misdiagnosed as major depressive disorder without psychotic features, depression not otherwise specified (NOS), or mood disorder NOS. It was quite striking that none of the patients with missed diagnoses were considered to have a psychotic disorder. This finding suggests that the clinicians were missing the psychosis rather than the mood disorder.

Distinction Between Psychotic Depression and Schizophrenia

By definition, in both DSM-IV and DSM-V, the psychotic symptoms in major Depressive disorder with psychotic features are episodic and occur only during an episode of major depression. In contrast, patients with schizophrenia exhibit psychotic symptoms that occur in the absence of an identifiable mood disorder. A family history of schizophrenia among relatives is not associated with an increased risk of psychotic depression.[26] A few biological markers have been documented that distinguish psychotic depression from schizophrenia.

Patients with psychotic depression and schizophrenia differ in hypothalamic-pituitary-adrenal axis activity and all-night sleep electroencephalogram readings.[1]

Somatic Treatment of an Acute Episode of Unipolar Psychotic Depression

International Guidelines

While guidelines have been published for the treatment of unipolar psychotic depression, there are unfortunately no studies or guidelines that support specific pharmacological regimens for the treatment of psychotic depression in patients with bipolar disorder.[27] Several treatment guidelines recommend either the combination of an antidepressant and antipsychotic or electroconvulsive therapy (ECT) as the first-line treatment for unipolar psychotic depression.[28] These include the American Psychiatric Association (APA),[29] the Canadian Network for Mood and Anxiety Treatment (CANMAT),[30,31] the Texas Medication Algorithm Project (TMAP),[32] and the World Federation of Societies of Biological Psychiatry (WFSBP).[33] The South African Society of Psychiatrists[34] and the Royal College of Australian and New Zealand College of Psychiatrists (RANZCP)[35] recommend the combination of an antidepressant and an antipsychotic as first-line treatment and ECT as second-line treatment, while the Danish Board of Health[36] recommends ECT as the first-line treatment and the combination of an antidepressant and antipsychotic as second-line treatment. The National Institute for Health and Clinical Excellence (NICE)[37] and the Dutch National Steering Committee on Multidisciplinary Guideline Development in Mental Health (DNSC)[38] recommend antidepressant monotherapy as the first-line treatment. No treatment guidelines recommend antipsychotic monotherapy as a treatment option for psychotic depression.

The recommendation of antidepressant monotherapy (in contrast to the combination of an antidepressant and antipsychotic) for the acute treatment of psychotic depression in the NICE and DNSC guidelines may in part stem from a 2005 Cochrane review,[39,40] which concluded that there was a lack of statistical evidence for the superior efficacy of the combination compared with antidepressant monotherapy. However, a more recent meta-analysis, which included several randomized controlled clinical trials published since the 2005 Cochrane review, concluded that the combination of an antidepressant and antipsychotic was significantly more effective than either antidepressant monotherapy or antipsychotic monotherapy for the acute treatment of psychotic depression.[41]

In the United States, despite the APA Practice Guidelines having recommended the combination of an antidepressant and antipsychotic for the acute treatment of psychotic depression since 2000,[1] studies have shown that only 5% of patients with psychotic depression receive an adequate combination of an antidepressant and an antipsychotic.[3] These findings show a persisting low rate of adequate treatment (dose and duration of medications) of psychotic depression and little change from a study published a decade earlier, which also reported inadequate dose and duration of medication treatment.[42] This may be related to the under recognition of the psychosis in these patients[2] (discussed above).

Specific Combinations of Medications Studied for the Acute Treatment of Psychotic Depression

In a recent meta-analysis of antidepressant and antipsychotic trials for the treatment of psychotic depression, Farhani and Correll pointed out that efficacy has been demonstrated only for specific medication combinations (and not others) and that there is a need for further studies to help elucidate the effectiveness of different combinations of medications.[41] Given this, it is important to keep in mind that the studies discussed below may not be generalizable to all patients with psychotic depression or all combinations of antidepressant and antipsychotic medications. I was able to identify 7 studies in the medical literature that have compared the combination of an antidepressant and an antipsychotic (see table 1) to treatment with antidepressant monotherapy, antipsychotic monotherapy, or placebo in well-designed, double-blind, randomized controlled trials.

Newer medications (selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor + second-generation antipsychotic)

1. Venlafaxine plus quetiapine[43]
2. Sertraline plus olanzapine[44]
3. Fluoxetine plus olanzapine[45]

Older medications (tricyclic antidepressant + first-generation antipsychotic)

1. Amitriptyline plus haloperidol, trimipramine[46]
2. Nortriptyline plus perphenazine[47]
3. Amoxapine, Amitriptyline plus perphenazine[48]
4. Amitriptyline plus perphenazine[49]

Newer Medications

Venlafaxine Plus Quetiapine. Wijkstra and colleagues[43] reported on a double-blind, randomized controlled study of 122 hospitalized patients (aged 18–65 years) with psychotic depression at 8 sites in the Netherlands. The patients were treated for 7 weeks with imipramine ($n = 42$), venlafaxine ($n = 39$), or the combination of venlafaxine and quetiapine ($n = 41$). Dosages used were the following: imipramine (dose adjusted to adequate plasma levels of 200–300 ng/ml), venlafaxine (maximum 375 mg/day), or venlafaxine-quetiapine (maximum 375/600 mg/day). The primary outcome measure was a response on the Hamilton Depression Rating Scale (HAM-D; ≥50% decrease and final score ≤14). Remission was defined as a

Table 1. Combinations of Antidepressant and Antipsychotic Medications With Demonstrated Efficacy in Randomized Controlled Clinical Trials

Study	Sample Size	Combination	Statistically Significant Results
Newer medications (SSRI or SNRI + SGA)			
Wijkstra et al, 2010[44]	122	Venlafaxine (V) + quetiapine (Q)	Response: VQ > V; VQ = imipramine Remission: VQ > imipramine; VQ = V
Meyers et al, 2009[45]	259	Sertraline (S) + olanzapine (O)	Remission OS > O in both younger (<60) and older (≥60)
Rothschild et al, 2004[46]	249	Fluoxetine (F) + olanzapine (O)	Reduction in HAM-D score: Trial 1: OF > O and placebo Trial 2: OF = O = placebo
Older medications (TCA + FGA)			
Künzel et al, 2009[47]	94	Amitriptyline (AMI) + Haloperidol (HAL)	Response: AMI + HAL = Trimipramine Remission: AMI + HAL = Trimipramine
Mulsant et al, 2001[48]	52	Nortriptyline (NOR) + Perphenazine (PER)	Response: NOR + PER = NOR
Anton and Burch, 1990[49]	46	Amitriptyline (AMI) + Perphenazine (PER) Amoxapine (AMOX)	Response: AMI + PER = AMOX
Spiker et al, 1985[50]	51	Amitriptyline (AMI) + Perphenazine (PER)	Response: AMI + PER > AMI or PER

Note: SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SGA, second-generation antipsychotic; TCA, tricyclic antidepressant; FGA, first-generation antipsychotic.

final HAM-D of ≤7. Response rates for imipramine, venlafaxine, and venlafaxine-quetiapine were 22/42 (52.4%), 13/39 (33.3%), and 27/41 (65.9%), respectively. For the primary outcome measure of response, the venlafaxine-quetiapine combination was statistically significantly more effective than venlafaxine; there were no statistically significant differences in the response rates between venlafaxine-quetiapine and imipramine or between imipramine and venlafaxine. Remission rates for the venlafaxine-quetiapine combination (17/41, 41.5%) were statistically significantly more effective than imipramine (9/42, 21.4%), with no statistically significant difference compared with venlafaxine (11/39, 28.2%) and no significant difference between imipramine and venlafaxine. The authors concluded that the combination of venlafaxine and quetiapine was more effective than venlafaxine alone on the primary outcome measure (response) and was well tolerated.[43]

Sertraline Plus Olanzapine. The largest study to date, the NIMH Study of the Pharmacotherapy of Psychotic Depression (STOP-PD) reported results that indicated that the combination of an antidepressant and an atypical antipsychotic medication was more efficacious than monotherapy with the atypical antipsychotic.[44] The study included 259 subjects with psychotic depression, 142 subjects ≥60 years old and 117 <60 years old. 129 subjects were randomized to combination treatment and 130 to olanzapine plus placebo. Remission was defined as a HAM-D score of ≤10 at 2 consecutive assessments without delusions, as classified by a schedule of affective disorders and schizophrenia delusion severity score of 1 at the second assessment when the 2-week HAM-D depression remission criterion was met. Subjects who achieved a HAM-D score of ≤10 for the first time at week 12 were assessed again at week 13 to determine whether the 2-week duration criterion for remission was met. The daily dosages of medications in the STOP-PD study were as follows: (1) 50 mg sertraline/placebo and 5 mg of olanzapine as tolerated, initially; (2) increased to 100 mg sertraline/placebo and 10 mg olanzapine by day 7; (3) increased to 150 mg sertraline/placebo and 15 mg olanzapine by day 14; and (4) 200 mg sertraline/placebo and 20 mg olanzapine allowed for residual symptoms. Treatment with olanzapine/sertraline was associated with higher remission rates during the trial than olanzapine/placebo (OR, 1.28; 95% CI, 1.12–1.47; $P < .001$). 41.9% of subjects who underwent combination therapy were in remission at their last assessment compared with 23.9% of subjects treated with monotherapy (Chi square = 9.53, $P = .002$). Combination therapy was comparably superior in both younger (OR, 1.25; 95% CI, 1.05–1.50; $P = .02$) and older (OR, 1.34; 95% CI, 1.09–1.66; $P = .01$) adults. Overall, tolerability was comparable across age groups. Both age groups had significant increases in cholesterol and triglyceride concentrations, but statistically significant increases in glucose occurred only in younger adults. Younger adults gained significantly more weight than older subjects (mean [SD], 6.5 [6.6] kg vs 3.3 [4.9] kg, $P = .001$). Although the STOP-PD study did not include a sertraline monotherapy arm, a previous open-label study[50] reported that patients with major depression with psychotic features had a markedly lower response rate to 200 mg of sertraline per day for 8 weeks than patients with nonpsychotic depression.

Fluoxetine Plus Olanzapine. In 2 randomized, placebo-controlled trials,[45] a combination of the selective serotonin reuptake inhibitor fluoxetine plus the second-generation

antipsychotic olanzapine was compared with olanzapine monotherapy or placebo in 229 hospitalized patients with psychotic depression. These 2 studies are the largest randomized controlled trials for the treatment of psychotic depression that included a placebo arm. In both studies, patients were randomized to placebo, olanzapine (mean doses: 11.9 and 14.0 mg/day) plus placebo, or olanzapine (mean doses: 12.4 and 13.9 mg/day) plus fluoxetine (mean doses: 23.5 and 22.6 mg/day) and followed for 8 weeks. The first trial showed a reduction in HAM-D score that was statistically greater in the combination group than in the olanzapine monotherapy group or the placebo group throughout the 8 weeks. The second trial failed to reveal any statistically significant differences between the 3 treatment groups except for the HAM-D score in the combination group that was statistically lower than the placebo group at the end of week 1. However, there were several aspects of the study design that were biased against the combination of fluoxetine and olanzapine. First, the study was powered to show a difference between olanzapine monotherapy and placebo and not the combination therapy, resulting in a small sample size in the combination group, which limited statistical power. Additionally, the study design limited fluoxetine dosing according to olanzapine dosing, such that most subjects received only a starting dose of fluoxetine (20 mg/day). It is plausible that if higher doses of fluoxetine had been used, it could have produced greater reductions in depressive symptoms or higher response or remission rates.

Older Medications

Amitriptyline Plus Haloperidol. In a double-blind, randomized, multicenter trial, Künzel and colleagues[46] compared the effects of trimipramine monotherapy (n = 33) vs a combination of amitriptyline and haloperidol (n = 24) in patients with psychotic depression. At week 6, the mean dosages (±SD) were 356.1 ± 61.2 mg trimipramine, 184.0 ± 23.6 mg amitriptyline and 6.3 ± 1.8 mg haloperidol. No significant differences were found in rates of response and remission between the 2 groups. A possible explanation for the fact that no differences were found between the 2 groups is, as the authors themselves point out, that a high dosage of trimipramine was compared with a lower dosage of amitriptyline (combined with haloperidol).

Nortriptyline Plus Perphenazine. Mulsant and colleagues[47] compared in a double-blind trial the efficacy of nortriptyline plus perphenazine vs nortriptyline plus placebo in a group of older inpatients who presented with a major depressive episode with psychotic features. Fifty-two patients (mean age: 72) were included in the trial and started openly on nortriptyline that was titrated to yield a therapeutic plasma level (target: 100 ng/ml; range: 50–150 ng/ml). After 2 weeks, patients who had not responded were randomly assigned to addition of perphenazine (n = 17) or placebo (n = 19). The doses of perphenazine/placebo were titrated up to a maximum dose of 24 mg/day (mean dose: 18.9 mg/day) until patients showed therapeutic response or extrapyramidal side effects were detected. After patients had received nortriptyline for at least 4 weeks combined with either perphenazine or placebo for at least 2 weeks (median: 9 weeks), no statistical differences were observed on the HAM-D or the psychoticism subscale of the Brief Psychiatric Rating Scale (BPRS). Rates of response to nortriptyline plus perphenazine (50%) and nortriptyline monotherapy (44%) did not statistically differ among the 30 treatment completers (P =.99).

Amoxapine/Amitriptyline Plus Perphenazine. Anton and Burch[48] conducted a randomized, double-blind investigation that explored whether the efficacy of combination amitriptyline plus perphenazine could be matched by monotherapy with amoxapine, an antidepressant derivative of the antipsychotic medication loxapine, with dopamine antagonist activity. Using a 50% reduction in HAM-D score as criteria for response yielded response rates of 71% and 81% for amoxapine and amitriptyline plus perphenazine, respectively. Extrapyramidal symptoms were significantly more frequent in the amitriptyline plus perphenazine group than in the amoxapine treated patients.

Amitriptyline Plus Perphenazine. Spiker and colleagues[49] compared the combination of amitriptyline and perphenazine with amitriptyline alone and perphenazine alone in the treatment of patients with psychotic depression over a 5-week period. Using a 50% reduction in HAM-D and BPRS total scores and a final HAM-D score of less than 12 as response criteria, 14 of 18 patients (78%) treated with the combination responded, in contrast to 7 of 17 patients (41%) treated with amitriptyline alone, and 3 of 16 (19%) patients treated with perphenazine alone.

Augmentation Strategies. Lithium augmentation of antidepressants for nonpsychotic depression is a well-known strategy, particularly for partial responders.[51] However, lithium augmentation has not been adequately studied in the treatment of psychotic depression. In 4 small uncontrolled studies, lithium augmentation of the antidepressant/antipsychotic combination appeared to add additional efficacy, particularly in bipolar patients.[52–55]

The use of other augmentation strategies or the use of lithium augmentation with other combinations of antidepressant and antipsychotic medications has not been studied. Of note, augmentation with lithium is recommended by the APA, TMAP, and RANZCP guidelines when the initial pharmacological regimen fails to achieve full remission. The other guidelines do not mention

lithium augmentation in the section that discusses the treatment of psychotic depression.

Electroconvulsive Therapy (ECT)

ECT is advocated by most guidelines for the treatment of psychotic depression as being at least equally as effective as the suggested pharmacological first-line treatment. Only NICE, RANZCP, and DNSC place ECT as a third and final option to be used when other treatments have failed, or if acute response is required due to medical comorbidities or suicidality.[28]

The literature on the relative efficacy of ECT compared with pharmacotherapies is limited by a lack of prospective, controlled trials. Meta-analysis may offer the best opportunity to synthesize published treatment outcomes; however, it is difficult to draw broad conclusions from these studies because the ECT treatment was often compared with several different combinations of medications at varying doses and for different periods of time.[56]

In a review of 17 prospective and retrospective studies comprising 597 patients with psychotic depression by Kroessler,[57] response rates were 82% for ECT and 77% for the combination of a TCA and antipsychotic, with considerably lower response rates of 51% and 34% for antidepressant monotherapy or antipsychotic monotherapy, respectively. A second larger meta-analysis, which included data from 44 prospective and retrospective studies published between 1959 and 1988,[58] found that ECT was significantly more effective than TCA alone, with effect sizes of 2.30 and 1.16, respectively. The combination of an antidepressant and antipsychotic was found to have an intermediate effect size of 1.56, which was not significantly different from the other 2 groups.[58] The early initiation of ECT within 5 days of admission has been reported to shorten lengths of stay and reduce treatment costs[59] although hospital treatment with ECT is associated with longer lengths of stay when treatment is not instituted rapidly.[59–61] Some studies suggest that ECT may be even more effective for psychotic depression than for nonpsychotic depression.[61–65]

In clinical practice in the community, much lower ECT remission rates have been reported than in clinical trials of ECT.[66] For example, the intent-to-treat remission rates from a large cohort of adults treated with ECT in community facilities were in the range of 30%–47%.[66] The low rates of remission are of particular concern given the poor outcomes of patients who do not remit with ECT.[66] The low remission rates in community practice might be explained by the fact that patients with comorbid psychiatric and medical conditions that are associated with poorer ECT outcome might represent a larger proportion of the clinical population than the patients studied in clinical trials of ECT.[66]

The use of ECT as a first-line treatment for psychotic depression appears to depend on whether the patient is suicidal. In a survey of Danish psychiatrists, 21% said they would use ECT as a first-line treatment in nonsuicidal patients with psychotic depression.[28] However, if the patient was at high risk of suicide, 59% would use ECT as the first-line treatment.[28]

Psychotherapeutic Treatment of an Acute Episode of Unipolar Psychotic Depression

The development of psychotherapeutic treatments for psychotic depression is in its early stages as patients with psychotic features have been excluded historically from psychotherapy trials of depression. Given the significant morbidity and mortality associated with psychotic depression, psychosocial treatments for patients with psychotic depression are urgently needed. Several studies suggest the potential utility of psychosocial interventions for the treatment of psychotic depression.[67–77]

Behavioral activation (BA)[78] and Acceptance and Commitment Therapy (ACT)[79] are 2 new approaches that show considerable promise for treating patients with depression or psychosis. BA involves the identification of an individual's behavioral avoidance patterns via functional analysis (ie, examining antecedents and consequences of behavior) and the development of a goal-oriented plan for changing these behavioral deficits using a stepwise process.[78] The goal of ACT is to promote increased psychological flexibility through acceptance of unavoidable distress, cultivation of a mindful outlook (ie, awareness of mental events as products of the mind rather than literal truths) to counteract excessive entanglement with cognitions, and clarification of personal values linked to behavioral goals.[79] Acceptance-Based Depression and Psychosis Therapy (ADAPT) is an integration of the BA and ACT approaches and was developed specifically for patients experiencing severe depression with co-occurring hallucinations or delusions.[67] A recent open-label study of 14 patients with psychotic depression treated with ADAPT showed promise when combined with pharmacotherapy.[67]

Continuation and Maintenance Treatment of Major Depressive Disorder With Psychotic Features

Determining the optimal continuation and maintenance therapy for psychotic depression is of special concern due to the high rate of relapse observed in naturalistic follow-up studies of psychotic depression, including relapse after ECT.[80–82] Other concerns include a relapsing or chronic course,[83] high mortality rates,[83,84] a high risk of extrapyramidal symptoms and tardive dyskinesia with first-generation antipsychotics,[85] risk of metabolic syndrome with atypical antipsychotics,[44] an increased use of healthcare services,[15] and a high rate of disability.[15]

There is only 1 published randomized controlled trial of continuation pharmacotherapy for psychotic depression.[86] In this study, the benefits and risks of combination pharmacotherapy with nortriptyline or sertraline plus perphenazine were compared with those of antidepressant monotherapy with nortriptyline or sertraline during a 26-week period in 28 older patients with psychotic depression who had remitted after being treated with ECT. Overall, 25% of patients relapsed during the 26-week trial, 33% in the combination therapy group, and 15% in the monotherapy group. The difference was not statistically significant most likely due to the small sample size.

In an open-label maintenance study, Rothschild and Duval[87] assessed the effect of discontinuing the antipsychotic medication in patients with psychotic depression. Thirty patients with the diagnoses of unipolar major depression with psychotic features who responded to the combination of fluoxetine and perphenazine were studied. If the patient was stable for 4 months on the combination, the patient was then gradually tapered off the perphenazine. After tapering of the perphenazine after 4 months of treatment with fluoxetine and perphenazine, 22 of the 30 patients (73%) did not exhibit signs of relapse over the next 11 months while remaining on fluoxetine monotherapy.

In another open-label maintenance study, Flint and Rifat[88] followed a group of patients older than 60 years with major depression with and without psychotic features for 2 years after remission of their index episode. The 68 patients with nonpsychotic depression were maintained on the treatment they had responded to in the acute phase (ie, a therapeutic dose of nortriptyline with or without lithium augmentation), while 15 of the 19 patients in the psychotic depression group were treated with ECT and then switched to nortriptyline. Patients with psychotic depression were significantly more likely to suffer a relapse or a recurrence than the nonpsychotic group (47% vs 15%, respectively, $P = .005$).

Wijkstra and colleagues[89] reported on a 4-month open-label follow-up of 59 patients with DSM-IV-TR major depressive disorder with psychotic features, aged 18–65 years, who had completed as responders an acute double-blind, 7-week trial with imipramine, venlafaxine, or venlafaxine plus quetiapine. Relapse rate was low (3.8%; 2/53). Six patients dropped out during the 4-month follow-up.

Taken together, these studies suggest that in a patient with psychotic depression who has responded to the combination of an antidepressant and antipsychotic, it would seem prudent to continue the treatment for maintenance. Once an episode of nonpsychotic major depression responds to antidepressant medication, it is recommended that the antidepressant be continued to prevent relapse and recurrence of depression.[90–92] However, it is not known whether the antipsychotic medication needs to be continued once an episode of psychotic depression has responded to combined antidepressant-antipsychotic treatment. On the one hand, premature discontinuation of antipsychotic medication has the potential risk of relapse of a severe, disabling disorder. On the other hand, the unnecessary continuation of antipsychotic medication exposes a patient to potential adverse effects. An NIMH study to address the question as to how long a patient with psychotic depression who is in remission needs to stay on the antipsychotic medication is currently underway[93] at Weill Medical College of Cornell University, the University of Pittsburgh School of Medicine, the University of Massachusetts Medical School, and the University of Toronto Department of Psychiatry (NCT01427608).

Unfortunately, despite the demonstrated efficacy of ECT in the acute episode of psychotic depression, there is often a rapid increase in depressive symptoms within days to weeks after the completion of a course of ECT[66,81,94] and much lower ECT remission rates (ie, 30%–47%) reported in community settings than academic medical centers.[65] In a randomized, double-blind study of maintenance pharmacotherapy of psychotic depression after successful ECT,[81] in which patients were assigned to maintenance therapy with nortriptyline monotherapy, nortriptyline plus lithium, or placebo, 50% of the patients relapsed within 6 months.

The one exception to the high rate of relapse in patients with psychotic depression successfully treated with ECT was a study in the Netherlands,[95] in which 29 responders to ECT were followed for 1 year. The frequency of relapse after 4 and 12 months was 3/28 (11%) at 4 months and 4/27 (15%) at 1 year.

Summary

In summary, psychotic depression is associated with significant morbidity and mortality but is underdiagnosed and undertreated. In recent years, there have been several studies that have increased our knowledge regarding the optimal treatment of patients with psychotic depression. The combination of an antidepressant and antipsychotic is significantly more effective than either antidepressant monotherapy or antipsychotic monotherapy for the acute treatment of psychotic depression. Most treatment guidelines recommend either the combination of an antidepressant with an antipsychotic or ECT for the treatment of an acute episode of unipolar psychotic depression. The optimal maintenance treatment after a person responds to either the antidepressant/antipsychotic combination or ECT is unclear particularly as it pertains to length of time the patient needs to take the antipsychotic medication. Unfortunately, the number of studies and number of tested antidepressant/antipsychotic combinations is quite limited. Clearly, more studies are needed to investigate other combinations that are commonly used in clinical practice along

with studies of maintenance treatment. Little is known regarding the optimal treatment of a patient with bipolar disorder who has an episode of psychotic depression or the clinical characteristics of responders to medication treatments vs ECT treatments. Thus, there remain many questions for future research. Those that seem of greatest importance include the following: (1) what is the optimal maintenance treatment after a person responds to either the antidepressant/antipsychotic combination or ECT; (2) what are the clinical characteristics of responders to medication treatments vs ECT treatments; (3) decision trees to delineate the second and third lines of treatment when the first treatment is ineffective; (4) the efficacy of bilateral vs unilateral ECT; (5) differences in response and side effects to medication treatments and ECT in younger vs older patients; (6) the role of maintenance ECT; (7) what is the optimal treatment of a patient with bipolar disorder who has an episode of psychotic depression; and (8) do other combinations of antidepressant and antipsychotic medications that are commonly used in clinical practice have efficacy? The answers to these questions would be of significant practical utility to clinicians treating patients with psychotic depression.

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