REVIEW ARTICLE

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Psychotic Major Depression
A Benefit-Risk Assessment of Treatment Options

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Contents

Abstract

Numerous studies in the past three decades have characterised 'psychotic major depression', a subtype of major depression which is accompanied by delusions or other psychotic features. Evidence from phenomenological and neurobiological investigations indicates that this is a unique disorder with clinical and biological characteristics that are distinct from those of nonpsychotic depression and from other psychotic disorders. Treatment studies have provided evidence of small placebo effects and good responses to electroconvulsive therapy or combination treatment with an antidepressant plus an antipsychotic agent. How-

ever, until recently, there were only a few small, prospective, double-blind, controlled trials investigating the efficacy of antidepressant-antipsychotic combination pharmacotherapy, yet this constitutes the currently accepted and most universally applied 'standard of care' for psychotic depression. Treatment guidelines have been based largely on uncontrolled investigations of electroconvulsive therapy and studies using tricyclic antidepressants and first-generation antipsychotic drugs, which are not frequently chosen as first-line agents today because of concerns regarding tolerability and risks. However, recent open-label studies and large controlled trials of newer antidepressants and antipsychotics have yielded very divergent results thus far, so that the best treatment approach remains elusive. This review discusses the phenomenology and treatment of psychotic depression with a focus on the benefits and risks of various treatment approaches. Problems with this literature are highlighted, and strategies for future research are suggested.

1. Rationale

This article reviews the literature on the treatment of psychotic depression, including pharmacological treatment strategies and electroconvulsive therapy (ECT). We provide an historical perspective, a discussion of the diagnosis and diagnostic pitfalls of this disorder, a critical review of the available literature, and recommendations regarding treatment approaches and future research. Relevant literature was identified through a MEDLINE search using the terms 'psychotic depression', 'depression', 'psychosis' and 'delusional depression'. The historical and clinical information are presented as an overview of the literature, and controlled treatment studies are reviewed in detail.

2. Historical Perspective

'Psychotic major depression' is currently defined by the revised fourth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR)[1] as an episode of affective illness that: (i) fulfils criteria for major depressive episode (either unipolar or bipolar; episode type single, recurrent or chronic); and (ii) is characterised by the concurrent presence of 'psychotic features' (i.e. hallucinations or delusions.) A brief review of the nosological and conceptual evolution of this disorder will help provide a context for the relatively limited clinical database and treatment guidelines available to date.

Systematic study of the phenomenology, course and treatments for psychotic depression has been limited by the fact that broadly accepted operational criteria for the disorder did not exist until 1980, when the third edition of the DSM (DSM-III) was published.[2] Previously, psychiatrists considered delusions in the context of depressed mood to be a somewhat nonspecific phenomenon that occasionally occurred at the severe end of the depressive disorders spectrum[3] or, when more bizarre in content, as a concomitant of the 'schizoaffective' form of schizophrenia.[4] Moreover, the term 'psychotic' was generally used to describe a syndrome of depression with an 'endogenous' or 'melancholic' nature, i.e. an onset and course that seemed unrelated to life events and more attributable to some underlying biological defect.[4] Glassman and colleagues[5] scrutinised the features of endogenously depressed patients who did not respond to the tricyclic antidepressant (TCA) imipramine and noted that many had mood-congruent or nihilistic delusions. This work led to the introduction of 'delusional depression' as a distinct subtype of depression.[6,7] This early category had as its key defining feature the presence of mood-congruent delusions, but not hallucinations or mood-incongruent psychotic symptoms, which were included in the third and subsequent editions of the DSM.

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In DSM-IV-TR,[1] psychotic depression is diagnosed as major depressive episode, severe with psychotic features; the psychotic symptoms may include hallucinations and may be mood-congruent or -incongruent. Thus, most studies conducted since promulgation of the DSM-III[2] criteria for the psychotic subtype have been conceptually aimed at understanding the same disorder that was described in the earlier literature as delusional depression, but they are based on a broader category which may involve substantial heterogeneity.[8] Of particular concern is the assessment of perceptual abnormalities, some of which may be dissociative, obsessional, or even factitious in nature, rather than true hallucinations. Such symptoms commonly occur in post-traumatic stress disorder (PTSD), borderline personality disorder, obsessive-compulsive disorder (OCD) and body dysmorphic disorder.[9,10] Similarly, these other disorders are often characterised by disturbances in thought content that can be mistaken for delusions, including obsessional thoughts and pervasive beliefs regarding a lack of personal safety that commonly occur in individuals with a history of trauma. As these disorders are frequently co-morbid with major depression, it can be difficult to determine which disorder is primary, and whether a subjectively reported abnormality of perception or cognition represents a true hallucination or delusion or whether it is better understood as an intrusive thought, dissociative experience, or a psychological response to acute or remote stress or trauma. Structured diagnostic interviews can be useful in this regard, as they require the rater to carefully diagnose or rule out these other disorders, but if the interviewer is not experienced with these alternative abnormalities of perception or thought content, they may be misinterpreted as psychotic symptoms.

In addition to diagnostic changes, differences in clinical and research practices may also have substantially affected the developing knowledge base on psychotic depression. While older reports tend to be based on small investigator-initiated studies, more recent investigations have been large trials supported by pharmaceutical companies; a large study supported by the National Institute of Mental Health is currently under way. Moreover, the shift toward outpatient management and shorter inpatient stays for clinical treatment and research has resulted in a tendency for these studies to recruit outpatients. Similarly, recent studies have tended to go beyond questions of efficacy (i.e. whether a treatment works) in order to place more emphasis on effectiveness (i.e. whether a treatment is useful in real-world situations). If psychotic depression is indeed a very severe condition often requiring inpatient treatment, however, large studies of outpatients may capture a phenomenologically distinct clinical entity from that studied in older investigations. Finally, it may be impractical in the outpatient setting to withdraw concomitant medications, and the resulting findings may be difficult to interpret given the possibility of effects of other drugs.

Taken together, these concerns identify challenges in comparing results of older investigations, which mainly studied the effects of ECT, TCAs and first-generation antipsychotics (FGAs), with those from more recent studies involving newer pharmacotherapies, as the populations of patients participating in trials from the two eras may differ in clinically meaningful ways. Newer studies may include cohorts that have more diagnostic heterogeneity, have less severe illness, and are treated with concomitant medications and psychotherapy.

3. Differential Diagnosis

Further complicating interpretation of the available database are reports, typically describing naturalistic or open-label treatments, on depressive syndromes in patients with primary psychotic disorders (e.g. schizoaffective disorder, depressed type; post-psychosis depression in schizophrenia; delusional disorder, somatic type). Making a proper diagnosis of psychotic major depression versus a schizophrenia spectrum disorder can be difficult,[11] particularly when the temporal relationship between the development of psychotic and depressive symptoms is unclear. It cannot be assumed, and in fact the available data do not suggest, that treatment strategies proven efficacious for primary psychotic disorders

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are appropriate or optimal for patients with psychotic major depression.

4. Psychotic Major Depression: Unique Characteristics

Investigators early in the 20th century noted that patients with delusional depression experience a more severe syndrome and course of illness than their nondelusional counterparts.[12] Numerous studies in the past three decades have further characterised the disorder. In reviews of this literature, Schatzberg and Rothschild[13,14] summarised findings associating the presence of psychosis in depression with greater severity of depressive symptoms, a larger number of suicide attempts, more frequent hospitalisations, and worse short- and long-term course than depressed patients without psychosis. Specifically, this disorder has been characterised by longer episode lengths and higher rates of relapse and recurrence than nonpsychotic depression,[15-17] and there is evidence of decrements in social and occupational function when depressive and psychotic symptoms have improved.[18,19] However, not all studies find evidence of greater psychosocial dysfunction in psychotic depression[20,21] and there is some evidence that psychosocial impairment may resolve over time.[18,22] Studies of the course and outcome of depression have demonstrated evidence of interepisode consistency of psychotic symptoms, with an increased likelihood that psychotic features will emerge in subsequent depressive episodes.[23] Importantly, patients with psychotic depression have a very low placebo response rate,[6,24] and most studies find that they respond less well to antidepressant monotherapy than patients with nonpsychotic depression (reviewed in section 8).

Numerous investigations have examined whether, in addition to differences in clinical course and treatment efficacy, psychotic depression has a distinct pattern of neurobiological abnormalities. Studies of hypothalamic-pituitary-adrenal (HPA) activity, dopamine and serotonin neurotransmission, electroencephalographic sleep patterns, structural brain imaging, and neuropsychological function have demonstrated a pattern of abnormalities that may be implicated in the pathophysiology of this unique disorder. The presence of psychosis in unipolar depression has been associated with increased findings of hyperactivity of the HPA axis, with a number of studies showing elevations of basal and provoked measures of plasma cortisol or adrenocorticotropic hormone.[25-30] Dysfunction of monoamine neurotransmission has also been associated with the disorder.[31-34] Several studies have found that patients with unipolar psychotic depression have lower concentrations of serum dopamine β-hydroxylase, the enzyme that converts dopamine to noradrenaline (norepinephrine), than patients with nonpsychotic depression.[31,35-38] Other studies have shown elevation of plasma dopamine[39] and plasma or CSF levels of the dopamine metabolite homovanillic acid[32,33,40] in patients with psychotic depression. In addition, there is evidence of increased plasma levels of noradrenaline[39] and CSF levels of 5-hydroxyindoleacetic acid in patients with psychotic depression.[40]

While elements of formal thought disorder seen in patients with schizophrenia are typically absent in psychotic major depression, studies of neuropsychological function have shown some consistent deficits and performance impairments, particularly in the domains of verbal memory, executive functioning and performance speed.[26,41-45] Brain imaging studies have pointed to strong associations between brain atrophy and the presence of psychosis in depressed patients,[45,46] perhaps reflecting the toxic effects of excess glucocorticoid activity on neuronal growth and survival.[47]

5. Benefit-Risk Assessment: General Considerations

The execution of large-scale clinical trials to rigorously evaluate the efficacy, safety and relative utility of various treatments for psychotic depression remains a considerable challenge in view of the severity of this illness and the expense of conducting such research in inpatient care settings. The nature of ECT makes it extraordinarily difficult to compare this modality with pharmacotherapies in a controlled fashion. As a result, the field suffers from a

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paucity of empirically derived data to inform treatment guidelines for psychotic major depression. Recent large studies of newer treatment approaches are expanding this database, but the changes in diagnostic and research practices over time discussed above may influence the findings.

Currently, there are no drugs, devices or treatments approved by the US FDA specifically for the treatment of major depression with psychotic features. Depending on severity of illness and issues of patient safety at the time of presentation for treatment, the initial step in assessment of treatment options may include a decision about whether ECT should be initiated. ECT may be delivered alone or in combination with pharmacotherapy. Pharmacotherapy most commonly involves a combination of antidepressant and antipsychotic agents, although some studies have explored monotherapy with antidepressants, second-generation antipsychotics (SGAs) or antiglucocorticoid agents. Selection among newer agents (i.e. selective serotonin reuptake inhibitors [SSRIs], newer dual-action antidepressants, SGAs) or older agents (i.e. TCAs, FGAs) requires balancing evidence-based information on efficacy against concerns about tolerability and cost. As with other types of recurrent mood disorders, the best treatment decisions for psychotic major depression can be made after consideration of the following: efficacy data, drug or somatic treatment tolerability profile (short- and long-term adverse effects), relevant compliance issues (cost, dosing requirements, office visits), and continuation and maintenance phase strategies for prevention of relapse and recurrence. These issues are reviewed for specific treatments in detail in sections 6–12.

In addition to the present guidelines, resources for the physician making treatment decisions for psychotic major depression include expert consensus practice guidelines for treatment of unipolar[48] and bipolar[49] depressive episodes, evidence-based treatment algorithms for major depression,[50] and an educational website specifically addressing the characteristics and treatment of psychotic depression.[51] The process of educating patients and their families about the relative merits and possible adverse events related to somatic and drug therapies may be aided by printed information, videos or websites that summarise, in language appropriate for lay people, the nature of the illness and the available treatments. Such materials are readily available for major depression, but few organisations specifically cover psychotic depression in their materials.

6. Electroconvulsive Therapy (ECT)

ECT involves the application of an electrical current via scalp electrodes to induce a brief tonic-clonic seizure in anaesthetised patients within a medically controlled setting. ECT is widely considered the gold standard treatment for psychotic major depression. It is regarded as a highly effective and safe treatment for major depression, and some studies suggest that it may be even more effective for psychotic depression than for nonpsychotic major depression. An open-label retrospective study of response to an acute course of unilateral or bilateral ECT in 30 patients with psychotic unipolar major depression (defined by the Research Diagnostic Criteria [RDC]) compared with 36 patients with nonpsychotic depression yielded response rates of 83% for the psychotic group compared with 58% for patients without psychosis (with response defined as a score of ≤10 on the 17-item Hamilton Depression Rating Scale [HDRS]).[52] Petrides and colleagues[53] conducted a larger prospective investigation of the response to an acute course of bilateral ECT in 77 patients with psychotic unipolar depression compared with 176 patients with nonpsychotic unipolar major depression. Psychotic depression was defined according to the Structured Clinical Interview for Diagnosis for DSM-IV (SCID-IV) and a 24-item HDRS score of ≥21. Rates of remission were 95% for the patients with psychotic depression and 83% for the nonpsychotic group, with remission rigorously defined as a score ≤10 on the 24-item HDRS measured after each of two consecutive treatments and a decrease of ≥60% from initial scores. Improvement in symptom ratings on the HDRS was more robust and tended to be more rapid in the patients with psychotic depression than those with-

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out psychosis. A recent meta-analysis investigated the moderating effect of psychotic symptoms on the response to ECT in major depression.[54] This analysis, which included studies published between 1978 and 2001 that compared the efficacy of ECT with another treatment, found that ECT was more efficacious for patients with psychotic depression than for depressed patients without psychosis.

The literature on the relative efficacy of ECT compared with pharmacotherapies is limited by a lack of prospective, controlled trials. Owing to the postictal state that acutely follows delivery of each treatment, truly blind sham-controlled conditions are difficult to achieve. Meta-analysis may offer the best opportunity to synthesise published treatment outcomes, with the caveat that they often comprise studies with methodological variability, and the individual studies themselves often have limitations such as diagnostic heterogeneity and the use of retrospective data. A review of 17 prospective and retrospective studies of a total of 597 patients by Kroessler in 1985[55] found response rates of 82% for ECT and 77% for combination TCA/FGA, with considerably lower response rates of 51% and 34% for monotherapy with an FGA or TCA, respectively. A second larger meta-analysis, which included data from 44 prospective and retrospective studies published between 1959 and 1988,[56] found that ECT was significantly more effective than TCA alone, with effect sizes of 2.30 and 1.16, respectively. Combination TCA/FGA treatment was found to have an intermediate effect size of 1.56, which was not significantly different from the other two groups.[56]

6.1 Adverse Effects and Limitations of ECT

Despite the apparent superior efficacy of ECT for the acute treatment of psychotic major depression, use of this treatment has been limited by a number of considerations, including acceptability,[57] accessibility,[58] cognitive adverse effects,[59] cost[60] and very high rates of early relapse.[61,62] As a result, psychopharmacological treatment is usually employed as the first-line approach.

7. Antidepressant Plus Antipsychotic Combinations

7.1 Combined Treatment with Tricyclic Antidepressants (TCAs) and First-Generation Antipsychotics (FGAs)

The available data indicate that combined treatment with antidepressants and antipsychotics may be as effective, or nearly as effective, as ECT and is associated with a different profile of limitations and adverse effects. A few small controlled studies have investigated the effects of combining a TCA with an FGA, and more recent large investigations have begun to study newer antidepressants and SGAs.

The first randomised, controlled trial of combination treatment for psychotic depression was conducted by Spiker and colleagues.[63] Primary major depression was defined by the RDC for diagnosis of major depressive disorder, primary subtype (with 17-item HDRS average score by two raters of >15), and the psychotic subtype was defined as the presence of an unambiguous delusion with severity rating of at least 4 out of 6 on a 6-point delusion severity scale of the Schedule for Affective Disorders and Schizophrenia (SADS). Subjects were admitted to an inpatient service and randomised to a double-blind 5-week course of amitriptyline (n = 17) or perphenazine (n = 16) alone or in combination (n = 18); there was no placebo control group. Response rates were 41% for amitriptyline, 19% for perphenazine and 78% for the combined treatment group, with response defined as an HDRS score of <7 and the absence of delusions (delusional score of 1).

A second controlled study involved 46 inpatients with DSM-III major depression with psychotic features in a 4-week, randomised, double-blind trial comparing combined treatment with amitriptyline and perphenazine to amoxapine, a drug thought to act as a combined antidepressant/antipsychotic agent by virtue of its tricyclic structure and antidopaminergic properties. Patients were randomised if after 4 days of placebo treatment they still met the DSM-III criteria, had an HDRS score of >18 and persistent delusions and/or hallucinations. Both

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groups showed significant improvements in HDRS scores and >50% improvement was seen for 81% of the combined amitriptyline/perphenazine group and 71% of the amoxapine group. The groups did not differ significantly.[64]

In a more recent double-blind investigation, 36 older patients with a DSM-III-R[65] diagnosis of major depression with psychotic features and 17-item HDRS scores of >17 were randomised to receive perphenazine (n = 17) versus placebo (n = 19) in addition to ongoing nortriptyline treatment (n = 17). Response to the treatment, defined as an HDRS score of ≤10 and scores of 1 or 2 on the Brief Psychiatric Rating Scale (BPRS) psychosis items, did not differ between the groups. Forty-four percent of the group that received nortriptyline alone were responders compared with 50% of the group that received perphenazine plus nortriptyline. These rates are comparable with those seen in other studies of TCA monotherapy. As the authors note, the discrepancy between these findings and those of previous studies may have been due to differences in study design such as the relatively lower perphenazine doses used or the inclusion of older individuals who may have had underlying neurodegenerative changes.[66] As discussed in section 7.3, a large National Institutes of Health (NIH)-sponsored randomised, controlled trial is currently being conducted which will examine whether there are differences in the treatment of psychotic depression in older compared with younger patients.[67]

7.2 Adverse Effects and Risks of Combined Treatment with TCAs and FGAs

In addition to the limitations posed by the adverse effects of TCAs and FGAs, combined treatment with these agents may also result in problematic drug interactions between the two drug classes. Adverse effects of TCAs include dizziness, sedation, tachycardia, orthostatic hypotension, cardiac conduction delays, dry mouth, blurred vision, constipation and urinary retention. Adverse effects of FGAs include drowsiness, hypotension, tachycardia, blurred vision, constipation, urinary retention, gynaecomastia, lactation, weight gain, leukopenia, extrapyramidal symptoms (including tardive dyskinesia) and neuroleptic malignant syndrome. Pharmacodynamic interactions between FGAs and TCAs may reflect additive enhancement of adverse effects that occur with each drug class. Pharmacokinetic interactions also frequently occur. In particular, thioridazine and perphenazine inhibit the 2D6 isoenzyme of the cytochrome P450 (CYP) system, while several drugs, including the TCAs, haloperidol, thioridazine and perphenazine, are substrates for this degradative isoenzyme.[68] As a result, plasma levels of both drug classes may be increased during concurrent treatment with agents which are metabolised by this isoenzyme. Combined treatment with these agents should be monitored carefully, and dose reductions may be required.

7.3 Combined Treatment with Selective Serotonin Reuptake Inhibitors (SSRIs)/Newer Antidepressants and Antipsychotic Drugs

As SSRIs and other newer antidepressants have largely superseded the use of TCAs and monoamine oxidase inhibitors (MAOIs) owing to improved safety and tolerability profiles, these agents are increasingly used to treat psychotic depression. Prospective open-label studies and retrospective chart reviews of treatment with these agents combined with an FGA[69-71] or the SGA olanzapine[72-74] have demonstrated response rates in the range of 60–70%.

Two large, identical, double-blind, placebo-controlled multicentre trials[75] were recently conducted at 27 sites to test the efficacy of 8 weeks of the combination of olanzapine (5–20 mg/day) plus fluoxetine (20–80 mg/day) versus olanzapine monotherapy (5–20 mg/day). Major depressive disorder with psychotic features was defined according to the DSM-IV, and a 24-item HDRS score of ≥20 was required. Subjects were hospitalised for at least 1 week following treatment initiation and could be discharged if they were clinically improved. In the first trial, 51 of 124 subjects completed the study. There were no differences between groups with regard to discontinuation for adverse effects or lack

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of efficacy. Response rates, defined as a ≥50% reduction in HDRS scores, were significantly higher for the olanzapine-fluoxetine combination group (OFC), at 64%, than for the olanzapine monotherapy group (35%) or the placebo group (28%). In the second trial, 59 of 125 subjects completed the study. There were no between-group differences with regard to discontinuation for lack of efficacy, but 22% of OFC subjects discontinued because of adverse events compared with 2% in the placebo group ($p = 0.005$) and 9% in the olanzapine monotherapy group (difference not significant). In this trial, neither the OFC group nor the olanzapine group was significantly different from placebo with regard to HDRS scores or response rates. As the OFC study investigators note, there was a high placebo response rate in both trials compared with the historically absent or very low rate for psychotic depression;[6,24] this suggests that the clinical characteristics and perhaps underlying disorders of these patients may have differed from those of older reports on psychotic depression. It is also of note that there were dramatic reductions in HDRS scores in the first week, and the responses levelled off after the first week or two in all groups in both studies. This pattern could be influenced by placebo effects, nonspecific effects of treatment, or the stipulation that subjects could be discharged from the hospital if they had achieved clinical improvement after the first week. However, any such effects would be likely to apply to all groups and would therefore not account for the statistically significant finding of OFC superiority over placebo treatment in the first trial.

A large, multicentre, NIH-sponsored, randomised, controlled trial to study the efficacy of combination therapy with sertraline plus olanzapine versus olanzapine monotherapy in patients with unipolar depression with psychotic features is currently under way. To be included in the study, patients must have an identifiable delusion confirmed by at least two clinicians, and exclusion criteria include a diagnosis of OCD, body dysmorphic disorder, bipolar depression and recent use of illicit drugs.[67] The requirement of an identifiable delusion and the exclusion criteria are important for reducing diagnostic heterogeneity and targeting psychotic depression as it has been defined previously. Results of this study as well as additional investigations of combined treatment with other newer agents are needed to support the use of SGAs in psychotic depression. Risperidone, quetiapine, ziprasidone and aripiprazole are now commonly used in clinical practice for this purpose,[76] but these agents have not been subjected to rigorous study for psychotic depression thus far.

7.4 Adverse Effects of Combined Treatment with SSRIs/Newer Antidepressants and Antipsychotic Drugs

Adverse effects of SSRIs and some of the other newer antidepressants include gastrointestinal complaints (e.g. nausea and diarrhoea), drowsiness, agitation and insomnia. These adverse effects are usually transient, and changes in the dose or schedule of drug administration can frequently ameliorate them. Sustained sexual adverse effects, including decreased libido, erectile dysfunction and dysorgasmia, can also be addressed via adjunctive medications or changes in the dosage. Weight gain may complicate treatment with some of these agents.

Common short-term adverse effects of SGAs include somnolence and increased appetite, but the most problematic adverse effects are substantial weight gain, impaired glucose metabolism and dyslipidaemia. These latter effects are of greatest concern with clozapine and olanzapine, and less so with risperidone and quetiapine.[77] Extrapyramidal adverse effects are much less frequent than with FGAs.

Pharmacokinetic interactions of the CYP isoenzymes can occur with newer antidepressants and FGAs or SGAs. Fluvoxamine is an inhibitor of the CYP1A2 isoenzyme for which haloperidol, clozapine and olanzapine are substrates, and fluoxetine and paroxetine inhibit the CYP2D6 isoform, which is necessary for the metabolism of several FGAs and SGAs.[68] Citalopram, escitalopram and sertraline are less likely to interfere with SGA metabolism, but the potential for inhibition exists even with these drugs. Decreased metabolism of SGAs can be addressed by using lower doses of the sub-

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strate medication when it is given in combination with an inhibitor.

8. Antidepressant Monotherapy

As discussed above, it was the observation of Glassman and colleagues that depressed patients with psychotic symptoms had a relatively poor response to TCA monotherapy[5,6] that provided the conceptual foundation for the disorder we now recognise as a biologically and phenomenologically distinct subtype of major depression. Subsequently, a meta-analysis of data from 1054 patients in 12 studies supported the notion advanced by Glassman and colleagues, with findings of a general TCA response rate of 35% among patients with psychotic depression, compared with 67% for patients with nonpsychotic depression.[78]

However, a more recent double-blind study using fixed blood concentrations of imipramine in inpatients with DSM-III-R major depression with delusions (n = 15) and without delusions (n = 37) found a 50% reduction in HDRS score in 9 of 13 (69%) patients in the psychotic group who completed the study compared with 14 of the 32 (44%) nonpsychotic completers.[79] In this study, subjects who had been randomised to imipramine treatment were selected from a larger double-blind study comparing imipramine and mirtazapine in subjects with major depression and an HDRS score of ≥18 after a 4-day single-blind placebo treatment. Psychotic depression was defined very rigorously in this study: patients with hallucinations were excluded, and psychotic depression was diagnosed when subjects had at least one 'definite mood-congruent delusion' as defined by the SADS. The authors reported the actual delusional thought content for each patient in the psychotic group which was characterised by persecutory or somatic delusions or delusions of guilt or sin. The authors raised the possibility that the fixed blood concentrations accounted for the difference compared with prior studies; however, a number of previous studies reported adequate drug doses and therapeutic plasma drug concentrations,[5,80-82] and Spiker and colleagues[82] found that the advantage of combined therapy remained after controlling for the higher blood TCA concentrations in the combined treatment group.

In addition to data from studies comparing patients with psychotic depression and patients with nonpsychotic depression, a number of retrospective and prospective investigations have compared different treatments for psychotic depression as described above.[55,56,63] Results of these studies indicate that TCA monotherapy, with the exception of amoxapine as discussed in section 7.1, is less efficacious than ECT or combined antidepressant-antipsychotic treatment for psychotic major depression.

One research group in Italy has reported on a number of studies showing a surprisingly high degree of efficacy with SSRI monotherapy, particularly fluvoxamine, with remission rates in the range of 60–85%.[83-87] These studies typically involved either open-label trials of an SSRI or double-blind trials comparing the response to two different SSRIs or venlafaxine (fluvoxamine [n = 59];[83] sertraline vs paroxetine [n = 46];[84] fluvoxamine [n = 49];[85] fluvoxamine plus placebo vs fluvoxamine plus pindolol [n = 72];[86] venlafaxine vs fluvoxamine [n = 28][87]). These studies included inpatients with a clinical diagnosis of DSM-III-R or DSM-IV major depressive episode with psychotic features involving mood-congruent or mood-incongruent hallucinations or delusions. In four of the five investigations,[83,84,86,87] approximately one-quarter to one-third had a diagnosis of bipolar disorder, and many of these patients were maintained on their long-term lithium treatment.[83,84] All of the studies involved the following methodology.[83-87] After 7 days of placebo run-in, the medication trials lasted for 6 weeks. There was no placebo control. Symptoms were followed with the 21-item HDRS and the Dimensions of Delusional Experience Rating Scale (DDERS). The stringent definition of response was an HDRS score of ≤7 or 8 and a DDERS score of 0, and analyses generally used the last observation carried forward (LOCF) approach. In addition to these studies, another Italian group has briefly reported preliminary results of a 6-week randomised pilot study of paroxetine (n = 29) versus fluvoxamine (n = 22) monotherapy for DSM-IV major

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depression with mood-congruent psychotic features.[88] Response rates, defined by a ≥50% decrease in HDRS scores using the LOCF approach, were 76% and 73%, respectively.

The response rates for many of these SSRI monotherapy trials were in the order of 80%. These rates are comparable to those seen with ECT and combined treatment with TCAs and FGAs, much higher than those seen in trials of these drugs for nonpsychotic depression,[89] and higher than the 60–70% response rates seen in the open-label studies of SSRI-antipsychotic combinations and the double-blind olanzapine-fluoxetine combination study discussed in section 7.3. The lack of a placebo control renders interpretation of the significance of these response rates problematic. Given the literature on the severity and response to treatment in psychotic depression, these findings are unexpected and raise the question of whether patients recruited in these trials differ clinically from those of prior studies. As psychotic depression was defined according to a clinical interview method, it is possible that the diagnostic criteria used to enrol subjects were not as homogeneous or stringent as those of prior studies. It is possible that inclusion of a substantial proportion of subjects with bipolar disorder could confound the study results, given the possibility of switching from depression into hypomania and the effects of concurrent lithium which may be an effective augmentation strategy for bipolar psychotic depression.[71,90,91] However, this cannot account for the findings because there were no significant differences in response rates between bipolar and unipolar patients in these studies. A potential mechanism of action for fluvoxamine and possibly sertraline in the treatment of psychotic depression has recently been suggested by Stahl.[92] In contrast to TCAs, fluvoxamine and, to a lesser extent, sertraline have a high affinity for the σ_1-receptor in rat brain. The σ_1-receptor is found in the cerebellum, cingulate nucleus, hippocampus, hypothalamus and pons. This receptor is thought to regulate the glutamatergic system, and σ ligands appear to have antipsychotic properties.[92] However, whether this mechanism could account for these surprising clinical effects remains an open question.

Results of a recent 8-week open-label study of sertraline monotherapy that was conducted in a university hospital in Egypt do not support the contention that SSRIs are uniquely efficacious in psychotic depression.[93] Subjects were inpatients who met DSM-IV criteria for major depressive disorder with or without psychotic features (n = 25 per group) and had a 17-item HDRS score of ≥22. Sertraline was titrated according to response to 200 mg/day over the initial 5 weeks. At the conclusion of the 8-week trial, 64% of the nonpsychotic patients met the criteria for remission (score of ≤7 on the HDRS) compared with 16% of the patients with psychotic depression. Similarly, 68% of the nonpsychotic patients met the criteria for response (≥50% improvement in HDRS score) whereas only 32% of the patients with psychotic depression responded to sertraline monotherapy.[93]

Another recent report described a small retrospective chart review and a small, 4-week, open-label, randomised, prospective study on the efficacy of nefazodone monotherapy versus combined treatment with amitriptyline and haloperidol in inpatients diagnosed with psychotic depression according to the International Classification of Diseases (ICD)-10.[94] In addition to delusions and hallucinations, psychomotor agitation and retardation are considered to be psychotic symptoms for this diagnosis.[95] Defining response as a ≥50% reduction in 21-item HDRS scores, 8 of 10 patients on nefazodone and 6 of 10 patients on combination therapy in the prospective study were responders, but the authors noted that patients who endorsed psychosis items on the BPRS had a poorer response to nefazodone monotherapy, and concluded that nefazodone monotherapy was insufficient in depression with "severe and prominent psychotic features."

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9. Antipsychotic Monotherapy: Second-Generation Antipsychotic Agents

SGAs are increasingly used to treat psychotic depression for both practical and theoretical reasons. On a practical level, SGAs tend to be better tolerated than the older agents, and although they have been associated with weight gain, dyslipidaemia and impaired glucose metabolism, they have a lower risk of tardive dyskinesia and other extrapyramidal adverse effects than the FGAs. From a theoretical perspective, many SGAs act as relatively potent antagonists at the serotonin 5-HT_2 receptor, a property that has been associated with antidepressant effects.[96] As a result, it has been suggested that SGAs may be particularly useful in psychotic major depression. Case reports and retrospective chart reviews of SGA monotherapy for psychotic depression have shown some promising results,[74,97-104] but the few existing controlled trials have been disappointing. In the two double-blind trials comparing olanzapine monotherapy with olanzapine-fluoxetine combination therapy and placebo[75] discussed in section 7.3, there was no difference between the olanzapine and placebo groups. Similarly, in a double-blind, multicentre, 6-week, parallel-group trial, Muller-Siecheneder and colleagues[105] found that patients with DSM-III-R psychotic depression who were treated with a combination of haloperidol and amitriptyline (n = 18) had significantly greater reductions in scores on the BPRS and the Bech-Rafaelsen Melancholia Scale than those treated with risperidone monotherapy (n = 16).

10. On the Horizon: Antiglucocorticoid Agents

10.1 Cortisol Synthesis Inhibitors

The observation that severe major depression is associated with dysfunction of the HPA axis, in particular hypercortisolaemia, has led to the investigation of antiglucocorticoid agents as treatments for this condition. Substances that inhibit cortisol synthesis, including ketoconazole, metyrapone and aminoglutethimide, have been investigated for the treatment of both psychotic and nonpsychotic depression. Several case reports and open-label studies with these agents have shown substantial antidepressant effects,[106-111] although other reports have been less encouraging.[112]

10.2 Adverse Effects and Risks of Cortisol Synthesis Inhibitors

Common adverse effects of cortisol synthesis inhibitors used at proposed antidepressant doses include abdominal pain, nausea, vomiting, dizziness and rash. Less common are the serious adverse effects of hepatotoxicity and adrenal insufficiency, which present significant obstacles to the routine use of these agents.

10.3 Glucocorticoid Receptor Antagonists

Another approach capitalises on the existence of two types of glucocorticoid receptors, with one type (GR II) that is occupied only at high levels of cortisol. Mifepristone, a steroid drug with antiprogesterone activity that is approved in the US as the abortifacient RU-486, is also a potent GR II receptor antagonist. It has little affinity for GR I receptors and does not appear to block peripheral cortisol activity.[113,114] Case reports of mifepristone treatment of patients with Cushing's syndrome have documented reversal of psychotic and depressive symptoms,[115-117] and one small 8-week open-label study using mifepristone 200 mg/day in patients with nonpsychotic chronic depression showed modest improvement in three of the four patients.[118]

Several small trials that evaluated the efficacy and tolerability of mifepristone treatment for psychotic depression have recently been published. Belanoff and colleagues[119] conducted a small 4-day, double-blind, placebo-controlled, crossover study of mifepristone 600 mg/day monotherapy in five patients with DSM-IV psychotic depression confirmed independently by two psychiatrists. Scores on the 21-item HDRS and the BPRS declined in the mifepristone treatment phase by an average of 25% and 33%, respectively, compared with an HDRS decrease of 5.8% and a BPRS increase of 6%

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in the placebo treatment phase; these differences were not statistically significant.[119,120] A second study, conducted at six academic centres, tested three doses of mifepristone in an open-label, 7-day design with 30 inpatients with DSM-IV major depression with psychotic features and a 21-item HDRS score of ≥18.[121] Patients were randomly assigned to one of three doses (50, 600 or 1200 mg/day), and any stable doses of antidepressant or antipsychotic medications were continued. A ≥50% reduction in HDRS scores was seen in 18% of patients in the 50 mg/day group (n = 11), 50% of the 600mg/day group (n = 10) and 33% of the 1200mg/day group (n = 9). For a 50% decrease in the positive symptom scale of the BPRS, these rates were 27%, 60% and 67%, respectively. However, statistical analyses were not presented for these results. A third study was recently published by an independent group of investigators in two sites in Egypt.[122] Twenty inpatients with a diagnosis of DSM-IV psychotic depression independently confirmed by two physicians and a 21-item HDRS score of ≥23 completed a 6-day open-label course of mifepristone 600 mg/day with an 8-week follow-up period. By week 4, 18 of the 20 patients met criteria for response (a ≥50% decline in HDRS scores), and 11 were in remission (HDRS score ≤7). At week 8 some patients improved further, while three relapsed. Most recently, Flores and colleagues[123] treated patients with psychotic depression with mifepristone 600 mg/day (n = 15) or placebo (n = 15) for 8 days in a randomised, double-blind study. Psychotic depression was diagnosed by a research psychiatrist via clinical interview and SCID data, and subjects were required to have a score of ≥21 on the 21-item HDRS and a score of ≥5 on the BPRS Positive Symptom Subscale (BPRS PSS). Patients were allowed to remain on any medications with stable doses for at least 2 weeks. Seven of 15 patients (47%) in the mifepristone group met the primary outcome criterion of 50% improvement in the BPRS PSS compared with 2 of 15 (13%) in the placebo group (p = 0.046). Thus, mifepristone may hold promise for the treatment of psychotic depression, but efficacy remains to be established.

10.4 Adverse Effects and Risks of Glucocorticoid Receptor Antagonists

The use of these agents for the treatment of depression is currently confined to research protocols. Possible adverse effects of mifepristone treatment include nausea, vomiting, diarrhoea and rash. In pregnant women, the drug could cause uterine bleeding and cramping along with termination of the pregnancy. Short-term treatment with mifepristone for psychotic depression has been well tolerated.[119,121,122]

11. Treatment Duration

How long to continue treatment in the maintenance period is an important issue in the management of psychotic depression, a disorder with high rates of relapse and recurrence. The available database regarding the duration of maintenance treatment is limited. A few investigations have evaluated the efficacy of maintenance pharmacotherapy for psychotic depression. A naturalistic follow-up study of 52 patients with delusional depression[124] found a >80% relapse rate over the first year after hospitalisation, with most relapses occurring when patients were medication-free or while tapering the antipsychotic drug. Rothschild and Duval[69] conducted an open-label maintenance study of fluoxetine and perphenazine treatment in 40 patients with psychotic unipolar depression who had responded to a 5-week acute course of these drugs. None of the patients relapsed during the 3-month full-dose maintenance period. Eight patients (27%) had signs of impending relapse after perphenazine taper and were restarted on perphenazine with good effect. Five of these patients were tapered successfully after 8 months of combined treatment and remained well during the 7-month follow-up period. Relapse was predicted by longer duration of the episode, higher number of previous episodes, earlier age at onset, and younger age at index episode. Following fluoxetine taper at 1 year, all but one patient remained well during the 3-month follow-up period.

Other studies in this area have differed markedly with regard to sample characteristics and treatment approaches. One of the SSRI monotherapy studies

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mentioned in section 8[85] had no relapses in the 6-month follow-up period while patients were continued on fluvoxamine, and only 5 of 25 patients relapsed over 2 years of maintenance therapy. One open-label study followed elderly patients who had responded to an acute course of treatment. Most of the patients had responded to an acute course of ECT (n = 15) and were treated with maintenance nortriptyline treatment. Eight (53%) of the patients relapsed over the 2-year follow-up period.[125] In a randomised, double-blind study of 29 older adults with remitted delusional depression following an acute course of ECT, subjects were treated with nortriptyline plus perphenazine (n = 15) versus nortriptyline plus placebo (n = 13). Over the 6-month follow-up period, 5 of the 15 patients in the active combination group relapsed (25%) versus 2 of the 13 patients in the nortriptyline plus placebo group (15%); there was no statistically significant difference between the groups.[126]

Thus, as with the acute treatment literature, there are disparate findings regarding continuation and maintenance treatment for psychotic depression. Older patients with psychotic depression may have different acute and maintenance treatment responses from those of younger patients, and the findings with SSRI monotherapy in both the acute and maintenance phases differ from those of other studies of antidepressant monotherapy. Treatment should certainly be continued if there are persisting residual symptoms, and a trial with a new agent or ECT may be warranted if such symptoms are bothersome or cause functional impairment. After remission is achieved, the available data indicate that antidepressant medication should be continued for at least 1 year and antipsychotic medication for a minimum of 4–8 months in first-episode patients. Assessment of the patient's course of illness should inform decisions regarding treatment duration, as a more virulent course predicts relapse and therefore warrants longer maintenance treatment. Finally, careful tapering and monitoring for emerging symptoms is critical.

12. Treatment Costs

Treatment duration obviously influences the cost of the treatment; cost is an important public health issue that can also have substantial individual impact and affect adherence to treatment recommendations. In addition to the direct costs of the medication or treatment, there may be costs related to adverse effects that require medical intervention or limit productivity. Moreover, treatment costs must be balanced against the morbidity of the disorder itself, which might typically include occupational, social, family and other role dysfunction, as well as the risk of suicide. Similarly, costs of treatment during the continuation and maintenance periods must be balanced against the likelihood of relapse or recurrence, with the attendant costs of acute illness, which may include hospitalisation.

ECT may be perceived as especially burdensome with regard to costs, given the need for a special unit with highly trained personnel, the perception that ECT requires prolonged hospitalisation, and the very high relapse rates observed when an acute course of ECT is not followed by ongoing treatment. However, strategies exist that may reduce the impact of some of these factors. Initiating ECT within 5 days of hospital admission has been shown to decrease both length of stay and treatment costs.[60] Following a successful course of ECT for major depression with maintenance pharmacotherapy[61] or maintenance ECT[127-129] can reduce relapse rates substantially, and maintenance ECT has been shown to result in a tendency toward lower healthcare costs than maintenance pharmacotherapy ($p = 0.08$[129]). Combination treatment with a TCA plus an FGA is relatively easy to deliver, and the cost of these medications is quite low. However, adverse effects may increase noncompliance rates and result in significant morbidity. Newer antidepressants are more expensive, but tend to be better tolerated and are generally safer than TCAs. SGAs have been generally deemed preferable to FGAs from the perspective of long-term tolerability and safety, but they are substantially more expensive, and both classes of drug can have significant long-term adverse effects

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that may lead to associated chronic medical conditions.

13. Conclusions

Several classes of treatment options exist for psychotic major depression. The evidence supporting these approaches is quite limited, and studies have differed widely with regard to patient selection, sample size, nature of the comparison groups and study design (e.g. retrospective vs prospective, open-label vs double-blind). No single treatment emerges as the best first-line therapy, and none has US FDA labelling specifically indicating use for psychotic major depression. The available data on efficacy support the use of either ECT or a combination of TCAs plus FGAs. There are also some data from retrospective studies and one prospective placebo-controlled double-blind investigation supporting the efficacy of newer antidepressants combined with FGAs or SGAs; however, results of one of the two largest placebo-controlled studies to date were negative for the combination of olanzapine and fluoxetine. Adding to the confusion are the unexpected reports from non-placebo-controlled studies that antidepressant monotherapy is highly efficacious in treating psychotic depression; these reports are not consistent with previous studies of TCA monotherapy or with a more recent study of SSRI monotherapy using a nonpsychotic depressed comparison group. The antiglucocorticoid agent mifepristone may be a promising new treatment, yet the available data for this agent are also quite variable.

These discrepancies may be explained, at least in part, by the substantial methodological differences between these investigations, including the large-scale changes in diagnosis and psychiatric clinical practice over the last few decades. 'Psychotic depression' as defined in the newer, larger studies may be less severe and more heterogeneous than in older investigations. Diagnostic heterogeneity would be expected to lead to variability in the findings if the treatment in question is only useful for a subset of the sample, a subset that may vary substantially between samples. Future research should focus especially on diagnostic rigor, and reports of such studies should include details regarding the nature of the psychotic symptoms. The use of structured clinical interviews is recommended to assess symptoms of depression and psychosis and to rule out the possibility that putative psychotic features are symptoms of other disorders such as PTSD, OCD or borderline personality disorder. Comparison with placebo control groups and nonpsychotic depressed patients is necessary to determine the clinical significance of the findings.

Currently there are very limited data on which to base important treatment decisions, decisions which may have a large impact on adverse effects, cost and risks, in addition to the central question of which treatment will be most likely to result in response and remission. Clinicians are left with the difficult choice between: (i) ECT or combined TCA and FGA, both of which are supported by considerable retrospective (but quite limited prospective) efficacy data, but which entail a significant adverse-effect burden; and (ii) second-generation antidepressants either alone or in combination with SGAs, which have limited and variable data supporting efficacy but a generally more acceptable adverse-effect profile. Patient characteristics and preferences may favour one approach over another, but the question of efficacy remains. An evidence-based approach to choosing the best available treatment for patients with psychotic depression awaits the completion of further research.

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