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Editorial

Psychotic major depression: challenges in clinical practice and research

M. Heslin and A. H. Young

Summary

Psychotic major depression is an under-researched and under-identified disorder. We highlight the major challenges both in clinical practice and in conducting research with people with this disorder. We also suggest which major issues need addressing to move treatment and knowledge of this disorder forward.

Declaration of interest

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ICD–10 classifies a depressive disorder with the presence of delusions, hallucinations or depressive stupor as a severe depressive episode with psychotic symptoms: also known as psychotic major depression (PMD).[1] Hallucinations and delusions may be mood-congruent (consistent with depressive themes, for example guilt, death, nihilism), or mood-incongruent (not consistent with depressive themes, for example persecution, delusions of control, thought insertion). Both DSM-IV-TR and DSM-5 have a similar definition.[2,3]

The point prevalence of PMD in the general population has been estimated at around 0.4% (4/1000)[4,5] compared with around 0.46% (4.6/1000) for schizophrenia.[6] Some research suggests that PMD may have a similar[7] or higher[8] incidence than other psychotic disorders such as schizophrenia although other research challenges this and the discrepancy is likely to be because of methodological differences.[9]

Few studies have investigated long-term outcomes in people with PMD. Those that have highlighted similar[10] or increased[11,12] risk of mortality compared with people with schizophrenia and increased mortality compared with people with bipolar disorder.[13–15] Further, research has found that in individuals with PMD there is an increase in suicide attempts compared with schizophrenia and bipolar disorder[16] as well as an increased risk of completed suicide compared with schizophrenia[17,18] and bipolar disorder.[13–15,18] A more recent study conducted over 10 years reported that people with PMD had better social and service use outcomes than people with schizophrenia, but were more likely to attempt suicide or self-harm.[19] This severe clinical picture highlights the need for prompt identification and treatment of PMD. However, this is exactly where there is a lack of knowledge and highlights an urgent need for more research.

Identification problems

The National Collaborating Centre for Mental Health[20] stated that PMD is often not diagnosed accurately because the psychosis may be 'subtle, intermittent or concealed'. Rothschild & Schatzberg[21] state that PMD is often confused with non-psychotic depression and other psychotic disorders and emphasised that patients with PMD are unlike other patients with psychosis as they frequently recognise that their thinking processes are flawed, are embarrassed and keep their unusual thoughts and feelings to themselves.

The difficulties with identification of people with PMD has been demonstrated by Rothschild and colleagues[22] who examined patient notes and found that out of the 130 diagnoses made for 66 patients only 65% of diagnoses were correct. Moreover, none of the patients with an incorrect diagnosis were diagnosed with a psychotic disorder indicating it is the psychotic features rather than the depression that is being missed but also suggest it may not be that they are missing symptoms entirely but do not recognise them as delusional (guilt, poverty, persecution are common). This is clearly a problem in clinical practice as lack of identification will lead to inappropriate treatment and possibly allow symptoms to worsen.

There have been multiple ways suggested to overcome this from asking the patient about any 'irrational worries' as a way to illicit psychotic beliefs without labelling thoughts as such, thus making the patient more comfortable in disclosing,[23] to asking permission to speak to the patient's family to try to elicit any unusual thoughts, unusual experiences or paranoia,[23] to using adapted assessment scales.[24–26] However, the sensitivity and specificity of these have not been tested sufficiently. Regardless of which method is used, these methods could aid not just secondary mental health services to identify patients with PMD and therefore, treat accordingly, but could also be used in primary care with any patients presenting with depression to rule out PMD.

Treatment gaps

There is a lack of evidence-based treatment options for PMD. Crebbin *et al*[10] state that people with PMD are a largely under-researched group. This lack of research on PMD is demonstrated by National Institute for Health and Care Excellence guidelines[27] in which the only paragraph on the treatment of PMD is: '1.10.3.1 For people who have depression with psychotic symptoms, consider augmenting the current treatment plan with antipsychotic medication (although the optimum dose and duration of treatment are unknown)'.

The update in 2010[20] added a clinical summary that stated that there was no good-quality evidence for pharmacological treatments of PMD as there are practical problems in recruiting sufficient

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numbers of patients with PMD and therefore, clinicians should consider lower levels of evidence, but the guidelines do not indicate what.

Parker *et al*[28] conducted a meta-analysis of studies comparing combination antidepressant–antipsychotic therapies *v.* electroconvulsive therapy (ECT) *v.* antidepressant alone or antipsychotic alone for treating people with PMD. The authors reported a trend for ECT being more effective than combination drug therapy and significantly more effective than tricyclic drugs alone. Antidepressant–antipsychotic combinations were more effective than antipsychotic or antidepressant alone but not significantly so. A more recent study reported a 95% remission rate in people with PMD following bilateral ECT[29] and another reported that psychotic features in patients with depression were associated with remission (odds ratio 7.18, $P = 0.032$) following treatment with ultrabrief right unilateral ECT.[30] However, neither of these studies compared ECT with antidepressant/antipsychotic medication thus limiting the conclusions about the best line of treatment.

Two decades on and the evidence base has progressed little. Farahani & Correll[31] conducted a systematic review and meta-analysis of trials comparing antidepressant *v.* antipsychotic *v.* combination treatment for people with PMD. They concluded that antidepressant–antipsychotic cotreatment was superior to both monotherapies but could not comment on specific combinations. Leadholm *et al*[32] reviewed nine international treatment guidelines and found that they had contrasting opinions on the optimal treatment for PMD. Six suggested antidepressant–antipsychotic combination therapy and three recommend antidepressant monotherapy. Five recommend ECT to be equally as appropriate as medication as a first-line treatment. In the latest guideline for treating depressive disorders from the British Association for Psychopharmacology,[33] an unspecified combination of antidepressant with antipsychotic is advised over antidepressant or antipsychotic alone, with a recommendation to consider ECT. The only guideline to mention the use of psychological therapies in people with PMD is the Canadian Network for Mood and Anxiety Treatments Clinical Guidelines[34] which states that 'psychological therapies are not indicated' for people with PMD.

Conducting research on effective and cost-effective treatments for PMD is clearly going to be difficult while we are still struggling to identify people with PMD. However, this is also compounded by the issue of diagnostic stability.

Diagnostic issues

Estimates of prospective diagnostic stability for PMD are wide ranging from 24 to 100%[35,36] compared with 50–100% for schizophrenia,[37,38] around 40% for non-psychotic depression and around 35% for bipolar disorder.[39] This wide variation in prospective consistency is likely because of the large amount of heterogeneity in the studies (i.e. different diagnostic tools, widely varying follow-up lengths, differing samples and differing quality). Studies that recruit case participants from non-first episode samples are effectively sampling prevalence cases in treatment, biasing the investigation towards those who are more unwell. If only studies based on an incidence sample are included,[7,10,40–42] the prospective consistencies are 47–95% for PMD, compared with 73–96% for schizophrenia. However, these estimates were taken over 6 months to 10 years. As might be expected, the reliability of PMD as a diagnosis is directly linked to the duration of follow-up with stability decreasing over time varying from 95% at 6 months to 48% at 10 years.[7,10,40–42]

Diagnostic stability appears to be linked with age. A study on risk factors for conversion from PMD to bipolar disorder reported that as the age at onset increased, the chance of changing to bipolar decreased.[43] Another study examined the progression from unipolar depression to schizophrenia and reported the strongest predictor of progression to schizophrenia included younger age.[44]

The diagnostic instability of PMD has implications for all research on PMD. When studying aetiology of a disorder, incidence samples are thought to be preferred because prevalence samples bias results towards those who are more unwell. However, when diagnostic instability is high, incident diagnoses are likely to change and therefore the results may no longer apply. Similarly, any study using baseline diagnoses are likely to be undermined when diagnostic change is taken into account.

This also raises the issue of what the diagnostic instability of PMD means. It is beyond the scope of this article to review the evidence and hypotheses about the meaning of diagnostic instability in psychiatry, but it is worth bearing in mind that diagnostic groupings are still a work in progress, and a major change in our categorisation of disorders could have a major impact on clinical decisions and research methodologies.

Measurement of severity

Measurement of severity of disorder is important as it allows monitoring of an individual and the progression of their disorder.[45] However, most instruments have been designed to evaluate one aspect of the disorder in PMD, psychosis or depression, but not both. In 2014, the Psychotic Depression Assessment Scale (PDAS) was created to measure the severity of PMD.[24] The scale was developed from relevant items from the 17-item Hamilton Rating Scale for Depression and the Brief Psychiatric Rating Scale. The PDAS has shown clinical validity, responsiveness and unidimensionality in the measurement of PMD severity.[24] The tool has been shown to be able to detect statistically significant differences in treatment effects in studies of medication efficacy in people with PMD.[25] Additionally, the PDAS may be able to be used as a PMD detection tool among patients with depression.[26,46]

Where to go from here

There are many questions that clinicians and researchers might ask about PMD that are not covered here such as whether PMD is a subtype of psychosis or depression, or a completely separate entity that needs a distinct diagnostic category.[21,23,47–53] However, it is clear, that there are some major challenges in advancing our knowledge about PMD. The major questions for clinical practice are: how do we better identify PMD and what are the most effective and cost-effective treatments. Current research challenges include the challenge of studying more representative samples, how to best identify people with PMD and how to improve diagnostic stability.

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