Considerations on the ICD-11 Classification of Psychotic Depression

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Introduction

Depression accompanied by psychotic symptoms is referred to as delusional or psychotic depression (PD). PD is classified as a subtype of severe unipolar depression/severe depression in bipolar disorder in the two current major diagnostic systems, namely the 10th revision of the International Classification of Disease (ICD-10) [1] and the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [2]. PD is prevalent [3, 4], underdiagnosed [5], undertreated [6] and has a high morbidity and mortality [7–9], but has received proportionally little attention compared with other less prevalent and less severe mental disorders [10].

Based on the detection of a number of biological, clinical, therapeutic and prognostic differences between PD and non-psychotic depression (non-PD), it was proposed that psychotic depression should be categorized as a distinct syndrome in the DSM-IV [11–15]. The arguments against classifying PD as distinct from non-PD were summarized in the DSM-IV Source Book [16] and, to our knowledge, have changed little since then. Based on this source, the DSM-IV Work Group on Mood Disorders concluded that the differences between PD and non-PD

were too vague to merit a further distinction between the two entities than that defined by the DSM-III-R (psychosis designated by a qualifying decimal point under the severity code) [17]. Therefore PD remained classified under severe depression in both the DSM-IV and the ICD-10.

During the DSM-IV/ICD-10 era a number of studies reporting significant differences between PD and non-PD have been published (for a review, see Rothschild [10]). Consequently, the discussion regarding the classification of PD goes on [18, 19] and is of the utmost importance at a time when the current diagnostic manuals are under revision [20, 21].

Below, we discuss the arguments in favour of and against classifying PD as a distinct syndrome under the affective disorders. In order to cover all aspects, the discussion will build upon the five criteria for the ‘valid psychiatric syndrome’ as defined by Robins and Guze [22] – here accompanied by a sixth criterion covering ‘treatment response’. Finally, based on this evaluation of the current evidence, we give an outline for a redefinition of PD for the upcoming 11th revision of the International Classification of Disease (ICD-11), which is due in 2015.

Clinical Description

PD is characterized by the presence of delusions and/or hallucinations in addition to depression. A typical case is a patient displaying anhedonia, psychomotor retardation, loss of interest, poor concentration and who is tormented by delusions of guilt, disease, worthlessness or impending disaster [10]. PD has a characteristic symptomatology which, apart from the psychotic features, involves a psychomotor disturbance (either agitation or retardation), rumination, insomnia [23, 24], cognitive dysfunction and perplexity more often than non-PD [15, 25–27]. A recent study has suggested that PD may also be accompanied by comorbid anxiety, somatoform and personality disorders more often than non-PD [28]. In recurrent depressive disorder a psychotic depressive episode often leads to subsequent psychotic episodes [7, 13] with similar delusional content [11, 29].

Regarding the course of disease, PD is associated with increased long-term psychosocial impairment [30, 31], increased rates of relapse [32] and higher levels of mortality compared to non-PD [9], possibly due to increased risk of suicide [8, 32, 33].

One of the arguments raised by the DSM-IV Work Group on Mood Disorders against the classification of PD as a distinct entity was that the number of psychiatric syndromes was already too high [16]. This profusion of syndromes has recently been documented by a publication on the use of ICD-10 diagnoses of mental disorders in Danish hospital psychiatry [34]. This study reported that 380 diagnoses of mental disorders were available (using only 3-digit diagnostic codes, e.g. F20.0 for paranoid schizophrenia) and that the majority of these were used very rarely. The number of diagnostic syndromes should obviously be kept to a reasonable minimum, but since PD is a rather prevalent disorder [3, 4, 10] and already defined in the diagnostic manuals, this argument seems misplaced in the discussion of defining PD as a distinct diagnostic syndrome.

Another counterpoint to PD being a distinct syndrome concerns the relationship between the severity of depression and the presence of psychosis. It has been suggested that the differences between PD and non-PD could reflect mere differences in depressive severity [16]. It also seems to be a common clinical assumption that psychosis is simply an indicator of the degree of severity in depression and that psychosis will eventually develop if a depression becomes sufficiently severe. This 'severity-psychosis' hypothesis is supported by some studies of PD [35, 36] and also underlies the current classification of PD in both the DSM-IV and the ICD-10, where

the disorder only figures as a subtype of severe depression. However, recent findings call into question this theory. These studies have demonstrated that episodes of PD are not necessarily 'severe' according to the number of depressive symptoms [25, 37] and that patients without any history of psychosis may experience non-psychotic depressive episodes of greater symptom severity compared to psychotic depressive episodes in patients with PD [38].

Laboratory Studies

One of the factors which kept the DSM-IV Work Group from separating PD from non-PD was that they considered the differences in biology between the two disorders to be too subtle [16]. During the DSM-IV/ICD-10 era a number of 'biological' studies have been carried out and the existence of differences between patients with PD and non-PD are now widely accepted [10], although confounding due to comorbidity may also play a role [39]. The most consistent difference involves the regulation of the hypothalamic-pituitary-adrenal axis. Patients with depression have a dysregulated hypothalamic-pituitary-adrenal axis [40], but the dysfunction is significantly more pronounced in patients with PD compared to patients with non-PD and also compared to patients with schizophrenia. This has been demonstrated consistently through increased rates of non-suppression in the dexamethasone suppression test and high levels of blood and urinary free cortisol [41–43]. Importantly, the differences persist when adjusted for depression severity [44] and appear to be some of the most robust findings in the entire field of biological psychiatry. It has even been suggested by the American Psychiatric Association, that the dexamethasone suppression test may have a potential clinical utility in differentiating PD from other psychoses, i.e. schizo-affective disorder, bipolar disorder and schizophrenia [45, 46]. In support of the pathophysiological role of the dysregulated hypothalamic-pituitary-adrenal axis in PD, the glucocorticoid antagonist mifepristone has shown promise for the treatment of PD in some studies [47–49], but not others [50, 51].

Patients with PD also have lower activity of the enzyme dopamine- β -hydroxylase than patients with non-PD [52, 53]. Dopamine- β -hydroxylase converts dopamine to norepinephrine, and the lower activity could result in increased levels of dopamine which has been hypothesized to contribute to the risk of developing psychosis in PD as outlined in the 'corticosteroid/dopamine hypothesis for psychotic depression' [54].

Delimitation from Other Disorders

The delimitation of depression (and thereby also PD) from other mental disorders (most importantly schizoaffective disorder and schizophrenia) is defined in both the ICD-10 and the DSM-IV criteria and is supported by findings from both family [55] and follow-up studies [56]. The focus of this paper is mainly the distinction between PD and non-PD, which is covered in detail above and below.

Follow-Up Studies

Another counterpoint to PD being a distinct syndrome concerns the stability of the diagnosis [16]. A very recent study has caused reason to question the validity of PD due to its finding of low diagnostic stability over 10 years [57]. However, this study is affected by several limitations (a very young sample, a large proportion of males and changing diagnostic instruments over time) and the findings are in contrast to a number of studies reporting high diagnostic stability of PD [3, 56, 58]. Furthermore, changes in diagnoses over time and so-called diagnostic drift exists for all mental disorders [59, 60] and for virtually all diseases in general [61, 62].

Family Studies

According to Robins and Guze [22], familial transmission of mental disorders is a prerequisite for the definition of a valid psychiatric syndrome: 'Independent of the question of etiology, therefore, the finding of an increased prevalence of the same disorder among the close relatives of the original patients strongly indicates that one is dealing with a valid entity.' A recent population-based family study has revealed that the familial transmission of mental disorders may be less specific than was previously assumed [63], i.e. having a parent with schizophrenia increases the offspring risk not only of schizophrenia and other psychotic disorders, but of all diagnoses across the spectrum of mental disorders. This finding illustrates that, if we accept a categorical diagnostic system, specific genetic transmission cannot be a rigid criterion.

Depression is heritable [64], but among the less heritable of the mental disorders, where schizophrenia and bipolar disorder lie at the other end of the spectrum [65]. However, studies have indicated that the heritability of PD is stronger than that of non-PD and that PD displays considerable specificity in familial transmission [55, 66–71]. This is consistent with the theory which implies that PD represents a more biological/primary disorder compared to non-PD [19].

Treatment Response

Another argument against the separation of PD from non-PD raised by the DSM-IV Work Group concerned the response to treatment: 'Still a number of questions can and should be raised about a separate designation ... particularly in regard to treatment, further prospective investigation is required' [16]. When this was written there was already a considerable body of literature showing that PD responded worse to both placebo and monotherapy with tricyclic antidepressants than did non-PD [11, 12, 15, 70, 72–75]. Since then only a few studies have compared the effects of psychopharmacological interventions in PD and non-PD. Two quite recent studies have not been able to confirm the previous differences in response, but should be interpreted within their limitations regarding external validity (study of an elderly population) [76] and lack of adjustment for baseline severity [77]. The general opinion remains that PD responds poorly to antidepressant monotherapy [10] and there is even some evidence suggesting that this regimen can exacerbate the psychotic dimension of the disorder [78, 79]. During the DSM-IV/ICD-10 era the treatment protocols comparing PD and non-PD have focused mainly on adjunctive psychotherapy and electroconvulsive therapy. The results of these studies indicate that PD responds poorly to psychotherapy [80, 81] but favorably to electroconvulsive therapy [82–84] compared to non-PD.

There is a growing body of evidence from recent randomized controlled trials, suggesting that the combination of an antidepressant and an antipsychotic is the superior pharmacological treatment approach in patients with PD [85–88]. In agreement with these findings, most major expert guidelines on PD recommend either electroconvulsive therapy or the combination of an antidepressant and an antipsychotic as first-line treatment [89–91]. This recommendation differs significantly from those for non-PD, where the augmentation with antipsychotics is generally reserved for depression resistant to at least two trials with antidepressant monotherapy [89–91].

Unipolar versus Bipolar Psychotic Depression

The studies referenced above are mainly based on patients with unipolar psychotic depression (UPD). However, there is a close relationship between UPD and bipolar disorder [10]. Patients with UPD are at high risk of converting to bipolar disorder [92–95], relatives of patients with UPD have higher prevalence of bipolar disorder compared to relatives of patients with non-PD [71, 94,

Fig. 1. Suggested ICD-11 definition of unipolar depression and bipolar disorder. The two figures outlined by a solid line define the actual diagnostic categories of bipolar disorder (corresponding to the current F31) and unipolar depression (corresponding to the current F32 and F33). The grey dotted line contains diagnoses that fall under the ‘meta-syndrome’ entitled PD. Each diagnosis is specified further depending on the presence of (1) hallucinations only, (2) delusions only or (3) hallucinations and delusions.

96], and unipolar depressed relatives of patients with bipolar disorders are more likely to suffer from the psychotic subtype than are unipolar depressed relatives of healthy controls [97]. A large number of studies have indicated that psychotic features are more prevalent in bipolar depression than in unipolar depression [98–101], but the literature published on the significance of psychosis in bipolar depression is somewhat sparse. However, equivalent to the case of UPD, it appears that the psychotic subtype of bipolar depression may also have implications for the symptomatology [102], treatment response [103], course of illness [104] and prognosis [105]. A study comparing patients with UPD and bipolar psychotic depression (BPD) did not detect any differences on a number of variables ranging from demographics to symptomatology [106]. Some studies of older date have suggested that patients with BPD may respond better than patients with UPD to the addition of lithium carbonate to the combination of an antidepressant and an antipsychotic [107, 108]. In the ICD-10, BPD is classified as ‘F31.5 – Bipolar affective disorder, current episode severe with psychotic symptoms’. Consequently, the ‘severity issue’ seems equivalent to that of the current definition of UPD.

Discussion and Perspectives

As outlined above, the number of studies reporting significant and clinically relevant differences between PD and non-PD has increased considerably over the past decades. This summary of the current evidence suggests that PD now fulfils the criteria for a valid psychiatric syndrome. The Task Force working with the classification of affective disorders in the upcoming 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) has acknowledged this development in their proposed revision, where the label ‘severe’ has been removed from ‘with psychotic features’. This means that PD will probably be classified at the same level as mild, moderate and severe depression without psychotic symptoms in the DSM-V [109]:

- 296.x1: mild depressive episode
- 296.x2: moderate depressive episode
- 296.x3: severe without psychotic features
- 296.x4: with psychotic features

where ‘x’ represents either ‘2’ (single depressive episode) or ‘3’ (recurrent depressive disorder).

Similarly, the severity criterion has been removed from the DSM-V criteria for BPD. We recommend that

this initiative is followed in the upcoming ICD-11. Our suggestion for the ICD-11 classification of depression with psychotic symptoms is illustrated in figure 1. Note that the current distinction between unipolar and bipolar disorders is maintained. The suggested modification allows the definition of a useful ‘meta-syndrome’ entitled ‘psychotic depression’ across the affective disorder chapter. The PD syndrome is defined by the diagnoses contained by the grey dotted line. Below we list the suggested ICD-11 diagnostic criteria for PD and the rules for sub-classification.

Diagnostic Criteria for PD in ICD-11

(1) General ICD-10 criteria for depression are fulfilled (duration, organic aetiology excluded). The distinction between the unipolar and bipolar branch depends on the presence of hypomanic, manic or mixed episodes prior to the current depressive episode.

(2) The ICD-10 criteria for at least ‘mild depressive episode’ are fulfilled (4 symptoms and at least 2 core symptoms).

(3) The first depressive episode with psychotic symptoms is labelled ‘first episode’ (the term ‘single episode’ leads to confusion). Subsequent depressive episodes with psychotic symptoms are labelled ‘recurrent’. This is also the case for the bipolar branch, based on the assumption that recurrence of psychotic depressive episodes is also a marker for poor outcome in bipolar disorder. This symmetry will also facilitate comparison of first episode/recurrent PD among patients with unipolar and bipolar courses of disease. Non-psychotic depressive episodes occurring in the period between 2 psychotic depressive episodes are classified in the unipolar/bipolar diagnostic categories outside the dotted square.

(4) Psychotic symptoms (delusions or hallucinations) are present, but diagnostic criteria for schizophrenia or schizo-affective disorder are not fulfilled. However, bizarre delusions or Schneiderian first-rank symptoms persisting for less than 2 weeks during a depressive episode can still be classified as PD if the depression is the predominant state. To avoid false-positive diagnoses of PD, only beliefs that have ‘delusional proportions’, i.e. defy credibility, and are withheld with ‘delusional intensity’, i.e. not changed by rational counterarguments, are classified as delusions [25].

(5) Mood congruence is evaluated based on the same criteria as suggested for the DSM-V [110]. Mood-incongruent psychotic symptoms are less prevalent than the

mood-congruent symptoms in PD [111, 112]. Some studies have indicated that mood incongruence predicts a severer course of disease compared to mood congruence [111, 113], but this remains controversial [25]. It has also been proposed that PD with mood-incongruent symptoms is a less stable diagnosis than PD with mood-congruent symptoms [114]. Therefore, at least until the significance of mood congruence is clarified, it seems appropriate to stratify PD based on this quality, which also seems to be the case in the upcoming DSM-V [110]. As in the DSM-V, mood-incongruent psychotic symptoms are given precedence over mood-congruent symptoms: if both mood-congruent and mood-incongruent psychotic features are present, the episode should be labelled as ‘mood-incongruent’.

(6) In addition to the evaluation of mood congruence, each diagnosis within the PD is further described according to the presence of: (a) only hallucinations; (b) only delusions; (c) hallucinations and delusions.

(7) The judgement of the severity of the syndrome as defined above should be based on a holistic evaluation of the clinical state taking both the depressive and the psychotic symptoms into account. A rating on a global severity/impairment scale seems more useful than the current rating, which is based on the mere number of symptoms. Ideally, a rating scale covering both the depressive and the psychotic dimensions of the disorder should be developed and validated for use in clinical research of PD. This scale could be constructed as a modified version of the Clinical Interview for Depression [115], which has demonstrated good clinimetric properties in the broad evaluation of affective symptomatology [116].

Note the suggested removal of stupor as a psychotic symptom in our definition of PD. In ICD-10, the only catatonic symptom classifiable under the affective disorders is depressive stupor, which has status as a psychotic symptom on a par with delusions and hallucinations [1]. However, other catatonic features like stereotypes, mannerisms or bizarre posturing can also accompany depression, but are not considered by the ICD-10. The current classification of depressive stupor as psychotic depression appears to be an unfortunate consequence of the lacking catatonia diagnosis in the ICD-10. Depression with stupor would not be labelled as PD according to the DSM-IV and the DSM-V, but, more informatively, as ‘severe depression with catatonic features’. It has recently been suggested that catatonia should be classified as a distinct syndrome, separate from the diagnoses of schizophrenia and mood disorders [117]. We believe that this suggestion

should be followed in the ICD-11. As a consequence, the catatonia diagnosis would also be applicable to the diagnosis of PD.

The vast majority of studies on PD, referenced in this paper, including the randomized controlled trials, have used the DSM-IV definition of PD as inclusion criteria. Consequently, the results of these studies are not valid for the cases of psychotic depressive episodes diagnosed according to ICD-10, where stupor is the psychotic determinant. The removal of stupor as a psychotic symptom in the ICD-11 would therefore be an advantage in research across the DSM/ICD border and increase the predictive value of future studies on PD.

Critics of the accentuated distinction between PD and non-PD outlined above would probably claim that many of the differences between the two subtypes are relative and not categorical. That might be true to some extent, but this is no different from shared phenomena between other mental disorders. For instance, symptoms of depression are common across the entire spectrum of mental disorders, but that has not precluded the nosological distinction between e.g. anxiety disorders and depression [1, 2]. Similarly, schizophrenia and bipolar disorders share risk factors, clinical features and response to the atypical antipsychotics [118], yet they are classified under two different chapters in the diagnostic manuals [1, 2]. Psychiatry as a field appears to have accepted that many symptoms of mental disorders are at least somewhat dimensional/continuous across the clinical syndromes [119–122]. However, we are not ready to cast the categorically defined disorders into oblivion because they aid significantly in communication among patients and health professionals, in clinical decision-making and in the definition of eligible subjects for research protocols etc. This is also reflected in the upcoming DSM-V, which appears to maintain the categorical backbone from the DSM-IV [110]. Consequently, the fact that PD and non-PD cannot be separated categorically from each other in every aspect is no different from many other diagnostic categories and should not preclude the definition of PD as a distinct syndrome.

What seems to be more important are the likely consequences of implementing the diagnostic changes suggested above. If we accept that PD fulfils the criteria for a valid psychiatric syndrome, does that merit the suggested change to the diagnostic classification? In our opinion, the short answer to this question is ‘yes’, simply because the advantages of doing so will outweigh the disadvantages, both for future clinical practice and for research purposes. PD is a prevalent [3, 4], underdiagnosed

[5] and undertreated [6] disorder. Clarifying the distinction between PD and non-PD in the diagnostic classification system would increase the focus on PD, encourage proper screening for psychosis among patients with depression and thereby decrease the high rate of missed diagnoses in current clinical practice [5]. If a larger proportion of patients suffering from PD are diagnosed properly, the overall burden of disease caused by the disorder is likely to decrease due to more targeted treatment. Furthermore, the advantages for future research appear to be several:

- increased number of eligible patients for clinical trials due to more focused diagnostics; this will create an increased incentive for researchers and pharmaceutical companies to engage in randomized controlled trials and other trials involving PD;
- facilitated research across the DSM/ICD border due to increased similarity between DSM-V and ICD-11;
- improved possibilities of investigating the significance of recurrence in BPD and across the unipolar/bipolar spectrum;
- increased power in all types of studies comparing PD with non-PD due to decreased rates of false-negative diagnoses of PD;
- enabled comparative studies of PD accompanied by only hallucinations, only delusions or both hallucinations and delusions.

We do not foresee any significant disadvantages caused by the suggested changes to the diagnostic classification. Obviously, the modifications would be followed by a period of adjustment, but even this should have limited consequences as no new concepts/nomenclature would be introduced.

Conclusion

PD fulfils the criteria for a valid psychiatric syndrome due to its distinct clinical presentation, neurobiology, heritability, prognosis and treatment response. We believe that the suggested redefinition of PD in the ICD-11 is merited and that such a revision will be of benefit to both research and clinical practice.

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