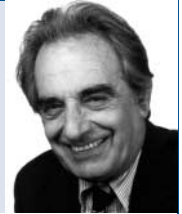


Editorial

Mixed features of depression:
why DSM-5 is wrong (and so was DSM-IV)

Athanasios Koukopoulos, Gabriele Sani and S. Nassir Ghaemi

**Summary**

The DSM system has never acknowledged a central position for mixed states; thus, mixed depressions have been almost completely neglected for decades. Now, DSM-5 is proposing diagnostic criteria for depression with mixed features that will lead to more misdiagnosis and inadequate treatment of this syndrome. Different criteria, based on empirically stronger evidence than exists for the DSM-5 criteria, should be adopted.

Declaration of interest

In the past 12 months, S.N.G. has received research grants from Pfizer and Takeda Pharmaceuticals, and has provided research consultation to Sunovion Pharmaceuticals.

Athanasios Koukopoulos (pictured) was born in Greece and lives and works in Rome. He has spent more than 50 years doing research in the field of mood disorders and has personally treated more than 10 000 patients. Gabriele Sani is a researcher at Sapienza University of Rome. His main clinical and research activity is in the field of mood disorders. Nassir Ghaemi is a professor of psychiatry at Tufts University School of Medicine and director of the mood disorders program at Tufts Medical Center in Boston.

The great British psychiatrist Aubrey Lewis once emphasised that a legitimate psychiatric nosology needs to be both useful and valid; one or the other is insufficient.¹ It appears that validity is less and less relevant to DSM revisions; utility has become the primary concern, especially a strong theoretical desire to avoid expanding psychiatric diagnoses so as to avoid ‘overdiagnosis’ of mental illnesses in the general population.² A clinically common and important example of this prioritisation of ‘pragmatic’ concerns over clinical reality is the phenomenon of mixed states in depression.²

DSM: the rejection of mixed states

In 1980, DSM-III³ divided Kraepelin’s broad concept of manic-depressive insanity (MDI) into two parts: bipolar disorder and major depressive disorder (MDD). This was not Kraepelin’s approach,⁴ which was that all recurrent mood illness, whether depressive or manic, was one illness – MDI. If a patient had ten depressive episodes, it was MDI; if a patient had ten manic episodes, it was MDI. The polarity – depression versus mania – did not matter. The recurrence of episodes, alternating with normality (or subsyndromal symptoms), was diagnostic. This is how Kraepelin phrased it:

‘The course of manic-depressive insanity is marked by a recurrence of attacks separated by lucid intervals . . . It seldom happens that all are of the same type; at some time or other a depressive attack is sure to appear . . . several depressive attacks may recur before a manic attack appears; in other words, the occurrence of several attacks of one type to the exclusion of other types indicates that the greater number of attacks throughout life will be of the same character.’⁵

As can be seen from this passage, Kraepelin clearly emphasised the importance of recurrence in general, rather than making a specific pole diagnostic.

Half a century after Kraepelin, Leonhard argued for polarity as the basis of diagnosis, distinguishing patients with unipolar disorder from those with bipolar disorder according to genetic and course findings – the bipolar/unipolar dichotomy.⁶ Later in the DSM-III process,⁷ mild, chronic versions of depression were

aligned with Leonhard’s severe episodic unipolar depression – producing that giant mish-mash entity of ‘major depressive disorder’. In this sense, then, the DSM-III nosology of mood is neo-Leonhardian, and not Kraepelinian.

There is an important consequence of this historical evolution. Because DSM-III insisted on polarity as the basis of diagnosis, it had to explain away mixed-mood states. Mixed states, by definition, involve the mixing of poles, which thus means that mood poles cannot be sufficiently distinguished to form the basis for diagnosis. If mixed states are common, then the entire DSM system for mood disorders falls apart. Kraepelin thought mixed states were frequent forms of mood episodes, hence the invalidity of polarity as the basis for diagnosing mood illnesses. (One must acknowledge that Kraepelin saw severely ill patients with psychosis in mental asylums; today’s out-patient practice setting is different, yet recent studies often are consistent with many of Kraepelin’s observations.)

According to DSM-III and DSM-IV,⁸ mixed states were seen as rare; this is because those diagnostic criteria made it difficult to diagnose them. This is most clear in DSM-IV, where mixed-mood episodes were narrowed compared with prior definitions by requiring the presence of full manic and depressive episodes at the same time. (These DSM-IV narrow diagnostic criteria for mixed states were not based on any scientific evidence.) This high threshold is met, according to empirical research, by only about 10% of mood episodes.⁴

Two decades of research since DSM-IV demonstrates the scientific limits of the DSM neo-Leonhardian error of ignoring mixed states. Yet, in acknowledging this evidence, DSM-5 may make the problem worse, because it proposes a new definition of mixed features in depression that is, once again, not based on empirical evidence – but, rather, on ‘pragmatic’ judgements.

DSM-5: the loss of agitation

The key problem with mixed depression in the DSM system is the insistence that the symptom of psychomotor agitation is diagnostically non-specific. This opinion is a matter of faith, assumed, rather than proven, within the DSM system. Since DSM-III, agitation has been listed as just part of the fifth criterion for a major depressive episode: ‘psychomotor agitation or retardation nearly every day’. This relegation of psychomotor agitation to a subcriterion has resulted in a clinical practice where the same diagnosis, major depression, is given to an extremely

agitated person as well as to a person with extreme psychomotor retardation.

The DSM-5 task force made the error of combining manic and depressive symptoms only where those symptoms do not overlap. This ‘non-overlapping’ criterion means that psychomotor agitation is excluded as a criterion of mixed features, as is irritability and distractibility (www.dsm5.org). Thus, DSM-5 defines mixed features of MDD as the presence of major depressive episodes with, most of the time during the episode, three or more of the following: euphoric mood, decreased need for sleep, grandiosity, flight of ideas, talkativeness, increased goal-directed activities and impulsive pleasurable behaviour with potential for painful consequences.

Mixed depression, in our research and experience as well as that of many others,^{9,10} is often characterised by markedly irritable mood and psychic or psychomotor agitation – the exact features excluded in DSM-5. This would be like proposing a new definition for migraine headaches, but excluding symptoms of pain in the head. Of course, one can have pain in the head from other conditions besides migraine, but why should this be a reason to exclude that symptom entirely?

Based on already available evidence, this DSM-5 approach can be demonstrably proven to be scientifically invalid. By requiring euphoric mood, along with depression (a logical contradiction) and excluding psychomotor agitation as diagnostically relevant, DSM-5 creates a clinical construct that is nowhere to be found. In empirical studies, the frequency of mixed-mood states similar to the DSM-5 definition ranges from 0 to 12%.¹¹

In contrast, using a definition that includes irritability, psychic or psychomotor agitation as central features of mixed depression, we and others have found frequencies ranging from 33 to 47% in replicated, large studies of patients with mood disorders.^{12,13} In our clinical practice, we have seen flight of ideas and talkativeness frequently in mixed depression, but the other five DSM-5 criteria are extremely rare, if ever present.

The verdict of history should also not be ignored. In Kraepelin’s careful descriptions, he described two forms of mixed depression: excited depression and depression with flight of ideas.¹⁴ Wilhelm Weygandt, in his famous 1899 monograph on mixed states, considered mixed states to be the most common version of manic–depressive illness, as recently analysed, occurring in 64% of patients at the Heidelberg clinic.¹⁵ Weygandt saw mixed states as an association of depressed mood with psychomotor excitement and flight of ideas, often with agitation. He mentioned elevated mood only in cases of a shift to pure or mixed manic/hypomanic states.¹⁵ In the writings of the classical authors (with two millennia of clinical experience) there is no mention of five of seven (excluding pressured speech and flight of ideas) DSM-5 mixed criteria.

Defining mixed depression scientifically

In our view, mixed depression does not mean DSM-defined manic and depressive symptoms happening simultaneously. It involves marked psychomotor agitation, inner anguish and irritability being central features of a depressive episode. The DSM-like manic symptoms, such as expansive mood, are sometimes reported along with depressive symptoms, but these relatively uncommon and brief mood states may be better conceptualised as mixed hypomania, rather than the common, longer duration states of mixed depression.

We believe it is a scientific and clinical error to exclude ‘overlapping’ mood symptoms from DSM-5 mixed features. Mixed states are frequent, and validly diagnosing and treating them is central to the practice of psychiatry.¹⁶ Yet our current

nosology practically ignores mixed states. The DSM-5 criteria, as they stand now, will make the scientifically valid diagnosis of mixed depression impossible, and we think that this will have severe consequences for patients. Our experience and research indicates that antidepressants are particularly harmful, and antipsychotics particularly useful, in mixed depression.¹⁷ By not capturing these patients in the restrictive DSM-5 definition, such patients will receive antidepressants, as they do now, which will worsen the agitation of this condition, and increase risk of suicide.

We propose, for depressive syndromes with psychomotor agitation, the traditional name of ‘agitated depression’ as in the original Research Diagnostic Criteria,¹⁸ the presence of at least two of the following manifestations of psychomotor agitation (not mere subjective anxiety) for several days during the current depressive episode: pacing; handwringing; being unable to sit still; pulling or rubbing on hair, skin, clothing or other objects; outburst of complaining or shouting; and overtalkativeness.

For mixed depressive syndromes without motor agitation, we propose the name ‘mixed depression’. Along with a major depressive episode, at least three of the following symptoms must be present: inner tension/agitation, racing or crowded thoughts, irritability or unprovoked feeling of rage, absence of signs of retardation, talkativeness, dramatic description of suffering or frequent spells of weeping, mood lability and marked emotional reactivity, and early insomnia.¹³

Mixed depression deserves its own diagnostic identity, with inner psychic agitation as its central feature, even if the DSM system needs to be overhauled in the process. Only then can we meet Aubrey Lewis’ challenge to be both useful and valid in our nosology.

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extra

Eleonora Fleury captured

Aidan Collins

In the history of the Medico-Psychological Association (MPA), precursor to the Royal College of Psychiatrists, the admission of the first female member in 1894 was surely one of the landmark events. It is surprising therefore that so little is known about Dr Eleonora Fleury and that the College has no image of her in its archive.

Eleonora (Norah) Lilian Fleury was born in Manchester in 1867. Her father was Charles Fleury, a surgeon. Her early education was likely to have been by home schooling, but she undertook her medical studies in London and Dublin, obtaining high honours at the MB examination of the Royal University of Ireland in 1890. She was the first female medical graduate from the Royal and was awarded the degree of MD (with Gold Medal) in 1893. The Royal was only an examining body and so she received her clinical instruction at the Richmond Hospital in Dublin and the London School of Medicine for Women. On qualification she worked at the Homerton (Fever) Hospital in London.

On her return to Dublin she took up a post as Clinical Assistant at the Richmond District Asylum at Grangegorman, then under the stewardship of Dr Conolly Norman and by far the biggest asylum in Ireland. Dr Norman appears to have had high regard for Fleury such that he proposed her for membership of the MPA in July 1893. Her election as a member did not pass on that occasion, but it was clear to most members of the council that women needed to be admitted to the association. The rule change was passed later in 1893 and in 1894 Dr Fleury became a full member. The admission of the first female to MPA membership was significant enough to be reported in the American medical press.

Fleury served as assistant medical officer in the Richmond Asylum and later deputy resident medical superintendent (RMS) at the satellite asylum at Portrane Co. Dublin. Conolly Norman died in 1908 and Dr Fleury did not fare well in the reshuffles that followed.

It has been said that she was passed over for the post of RMS either at the main asylum at Grangegorman or at Portrane because of her gender and certainly the annual reports display a tendency for the governors to prefer a male RMS, and even for a quota system to exist in terms of the number of female doctors allowed work in an asylum at any given time. Indeed, other women were not appointed to Portrane until Fleury's retirement in 1925. However, another factor may have hindered her advancement.

Irish Free State forces arrested Fleury during the civil war that followed the signing of the treaty with Britain in 1921. In 1923, she was detained in Kilmainham Gaol in Dublin. She had been involved in an organised assistance and escape programme for anti-treaty prisoners centred on the asylum at Portrane. While in Kilmainham she served as medical officer to the republican prisoners using whatever sparse resources were available to her. On her release she returned to her duties at Portrane.

The government that had imprisoned her remained in power until 1932.

Dr Fleury never married and she died in 1960. She spent the last years of her life in Rathmines, Dublin.



Taken during Fleury's early years at Grangegorman. She is included in a large group that includes Conolly Norman and his wife as well as Daniel Rambaut (later RMS at Northampton) and John O'Conor Donelan (later RMS at Grangegorman).

Image courtesy of St Brendan's Hospital Museum.