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Measuring mixed depression

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Abstract

Mixed states have long been recognised as being important in psychiatry. In this paper, we review the history of these concepts and recent developments in the field.

Keywords

mixed depression, mixed depression scale, mixed features

INTRODUCTION

The famous psychiatrist (Emil Kraepelin), together with his famous successor (Wilhelm Weygandt), thought that mixed states (i.e. combinations of manic and depressive symptoms) were the most common form of manic-depressive illness (Salvatore et al., 2002).

As the Diagnostic and Statistical Manual (DSM) nosology of mood disorders follows the conceptual system of Professor Leonhard and not that of Kraepelin (Koukopoulos et al., 2013), mixed states in general and mixed depression, in particular, have been neglected for decades.

Professors Leonhard and Kraepelin are two of the most important figures in the history of psychiatry.

In the most recent edition of DSM (DSM-5), the category "mixed episode" has been eliminated and replaced with the specifier "with mixed features". According to the DSM-5, mixed depression is diagnosed as the following (American Psychiatric Association 2013):

Full criteria for a major depressive episode (MDE) and at least three of the following hypomanic symptoms during the majority of days of the current or most recent depressive episode:

- Elevated, expansive mood
- Inflated self-esteem or grandiosity
- More talkative than usual or pressure to keep talking
- Flight of ideas or subjective experience that thoughts are racing
- Increase in energy or goal-directed activity
- Increased or excessive involvement in activities that have a high potential for painful consequences
- Decreased need for sleep.

Irritability, psychomotor agitation and distractibility were considered symptoms overlapping with other diagnoses and excluded from the DSM-5 definition of mixed depression (American Psychiatric Association 2013).

Such a definition poorly reflects reality. In an empirical study (Koukopoulos & Sani 2014), it was reported that the frequency of mixed-mood states, similar to the DSM-5 definition, ranged from 0 to 12%. On the contrary, when using a definition including psychomotor agitation, inner tension and irritability as central features of mixed depression, the frequency ranged from 33 to 47% (Koukopoulos et al., 2013).

Consequently, alternative sets of the frequently encountered and clinically relevant mixed features in depression were proposed by many authors. These focused on such mixed features as psychomotor agitation, distractibility, irritability, racing/crowded thoughts, increased talkativeness, emotional lability, inner tension, initial or middle insomnia and risky behaviours (Stahl et al., 2017). Among such alternative features were those proposed by Koukopoulos (Koukopoulos et al., 2013).

He recommended giving the name agitated depression to mixed depression with psychomotor agitation as defined by the research diagnostic criteria (Spitzer et al., 1978): the presence of at least two of the following manifestations of psychomotor agitation (not mere subjective anxiety) for several days during the current episode – pacing; hand-wringing; unable to sit still; pulling or rubbing on hair, skin, clothing or other objects; outburst of complaining or shouting; and over-talkativeness (Spitzer et al., 1978). He also proposed the name mixed depression for mixed depression without psychomotor agitation when at least three of the following symptoms are present along with an MDE: 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. In his explanation, he believed that the origin of psychic pain, agitation and other mixed symptoms in depression is an underlying excitatory process (Koukopoulos & Koukopolos 1999).

In clinical practice, we evaluated many patients with long-standing refractory depression (i.e. long-standing cycles of depressive episodes that do not remit using multiple types of antidepressants). All had been taking antidepressants for many years, and all complained of psychomotor agitation, inner tension/agitation and irritability as central features. None had a history of hypomania. The questions raised here were:

- Are these cases of unipolar depression that require more effective antidepressant treatment?
- Are these cases of bipolar depression that need mood stabilisers?
- Are these cases of the non-DSM excitatory (mixed) depression?

We were inclined to consider these symptoms consistent with the non-DSM excitatory (mixed) depression, and thus tapered their antidepressants and initiated treatment with a small dose of an antipsychotic. Surprisingly, a dramatic and fast response took place in most cases (Shahin 2017).

Given what is encountered in clinical practice, we suggest, like others (Koukopoulos & Sani 2014), that mixed symptoms of depression might be better called excitatory rather than hypomanic symptoms. Patients with excitatory (mixed) depression lack expansiveness and easy performance of activities. They are tormented by their psychic pain and unable to perform activities (Koukopoulos & Sani 2014). However, we are not inclined to abandon the DSM-5-defined mixed specifier or assume it is simply a kind of mixed hypomania as proposed elsewhere (Koukopoulos & Sani 2014). Additionally, one cannot claim, as it is the case in expansive "mixity", that excitatory "mixity" could be a marker of bipolarity. Instead, the negative impact of antidepressants on such symptoms is notable and hence we developed a novel scale to evaluate this; the Shahin Mixed Depression Scale (SMDS).

We recommend the routine use of SMDS in all apparently depressed patients in order to screen for possible clinically relevant mixed features. In addition, we recommend conducting further studies on what Koukopoulos named excitatory symptoms. We hypothesised that such excitatory symptoms could constitute a third subgrouping of bipolar disorder distinct from hypomania and depression or, at the very least, fall on a continuum between inhibited/retarded depression and expansive hypomania.

MANAGING MIXED DEPRESSION

Mixed depression should not be considered separately from the context of the whole disorder which could be unipolar depression or bipolar disorder. Additionally, one has to consider the following before planning for long-term management:

- Determine the current mixed features
- Consider whether the depressive context is unipolar or bipolar
- If unipolar, we would need to consider a possible bipolar diathesis.

The DSM-5 definition of mixed depression differs from the non-DSM-5 definition in which psychic and/or motor agitation, irritability and racing/crowded thoughts are central features. In practice, as stated before, we rarely encounter the DSM-5 mixed symptoms, except for the flight of ideas and pressure of speech (Koukopoulos & Sani 2014). If encountered, it might be seen as rather mixed hypomania (Koukopoulos & Sani 2014), prodromata for hypomania or an indicator of possible switching to frank hypomania. So, one must avoid using antidepressants in such cases and consider the bipolar diathesis, even if there is no history of hypomania.

In cases of the non-DSM5 mixed depression, a small dose of an antipsychotic alone at first is very rapidly effective in terms of both mixed symptomatology and the depression itself (Koukopoulos et al., 1992, 2004; Parker 2002). In some cases, just after the excitatory symptoms subside, a simple depression might set in and a course of an antidepressant could be necessary.

SUMMARY

In summary, based on the notion that a definition of mixed depression that will better predict the impact of a treatment is the definition of choice in clinical practice (Benazzi 2005), the non-DSM mixed features in depression should be considered important and clinically relevant. Screening for them using the SMDS (Shahin et al., 2020) is worth considering.

DECLARATION OF INTERESTS

Professor Allan H Young:
Employed by King's College London; Honorary Consultant SLaM (NHS UK). Paid lectures and advisory boards for the following companies with drugs used in affective and related disorders: AstraZenaca, Eli Lilly, Lundbeck, Sunovion, Servier, LivaNova, Janssen, Allergan, Bionomics, Sumitomo Dainippon Pharma, COMPASS. Consultant to Johnson & Johnson and LivaNova. Received honoraria for attending advisory boards and presenting talks at meetings organised by LivaNova. Principal Investigator in the Restore-Life VNS registry study funded by LivaNova. Principal Investigator on ESKETINTRD3004: "An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression." Principal Investigator on "The Effects of Psilocybin on Cognitive Function in Healthy Participants". Principal Investigator on "The Safety and Efficacy of Psilocybin in Participants with Treatment-Resistant Depression (P-TRD)". Grant funding (past and present): NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); NIHR (UK). Janssen (UK). No shareholdings in pharmaceutical companies.

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