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MOOD DISORDERS (SM STRAKOWSKI, SECTION EDITOR)

Activated Depression: Mixed Bipolar Disorder or Agitated Unipolar Depression?

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Abstract The combination of depression and activation presents clinical and diagnostic challenges. It can occur, in either bipolar disorder or major depressive disorder, as increased agitation as a dimension of depression. What is called agitation can consist of expressions of painful inner tension or as disinhibited goal-directed behavior and thought. In bipolar disorder, elements of depression can be combined with those of mania. In this case, the agitation, in addition to increased motor activity and painful inner tension, must include symptoms of mania that are related to goal-directed behavior or manic cognition. These diagnostic considerations are important, as activated depression potentially carries increased behavioral risk, especially for suicidal behavior, and optimal treatments for depressive episodes differ between bipolar disorder and major depressive disorder.

Keywords Agitation · Bipolar disorder · BD · Depression · Depressive disorder · Differential diagnosis · Mixed states · Psychomotor agitation · Suicidal behavior · Psychiatry

Introduction

It is easy to view depression and activation as opposites. Yet, depression and activation are often combined, with the potential for serious consequences, including poor impulse control and, especially, suicidal behavior. It is necessary to understand these combinations in order to understand, diagnose, and treat the diseases in which depression and activation occur.

Both activation and depression are complex constructs. Depression can be regarded as a disturbance that involves motivation, reward, and arousal. Depressive and manic affective states could be regarded as epiphenomena of these more basic disturbances [1]. Several authors have used multivariate analyses to identify orthogonal factors associated with depressive and manic states in clinical [2•, 3, 4] and even in nonclinical groups [5]. Mixed states were taken to represent co-occurrence of elevated factor scores associated with depression and mania [3]. Interpretation of activation adds diagnostic complexity. Activation is a prominent component of mania, as an expression of increased goal-directed activity in the service of disinhibited motivation and reward systems [6]. In the case of depression, activation can occur as a product of inner tension and anxiety, sometimes characterized as "psychic pain" [6] without being related to the increased goal-directed activity that characterizes mania.

These considerations lead to two limiting characterizations of activated depression. One is as mixed depressions, in which activation occurs as part of a manic syndrome combined with syndromal depression [7••]. This formulation has been taken to imply that, as activation is part of mania, activated depressions must therefore spring from bipolar disorder. A second is as agitated depression, in which the activation could potentially represent an aspect of the core depressive syndrome itself [8•], not necessarily requiring the activated depression to be a component of bipolar disorder. Because illness course and optimum short- or long-term treatment may differ between bipolar and unipolar disorders, and because of behavioral risks associated with activated depression, this question has practical ramifications. I will consider the following questions.

1. What are agitation and agitated depression?

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2. What are depressive mixed states, and how can depressive episodes of bipolar and unipolar disorders be differentiated?
3. What are mechanisms and consequences of activated depressions?

Agitation and Agitated Depression

What is Agitation?

The concept of agitated depression originally implied that agitation was a dimensional part of a core depressive syndrome. There are two potentially conflicting views of the relationship between agitated depression and mixed depressive states: the first is that agitated depression is perforce a mixed state of bipolar disorder, while the second holds that it is not. This dispute hinges in part on definitions of agitation.

Definitions of agitation are somewhat broad. Generally, both increased motor activity and inner tension are required, but the relative importance of the two constructs is generally not defined, and their definitions vary [9–11]. As we will discuss, many definitions conflate measures of goal-directed behavior, characterizing mania, with non-goal directed behavior, potentially more characteristic of depressive states.

Agitated depression stems from the older concept of melancholia agitata [11], which pre-dates the modern idea of bipolar disorder (BD). The Research Diagnostic Criteria defined agitated depression as a type of major depressive episode, which could be either major depressive disorder (MDD) or BD, characterized by at least two of pacing, handwringing, inability to sit still, pulling on or rubbing hair, skin, or clothing, outbursts of complaining or shouting, or inability to stop talking [12]. Analysis of behavioral and symptom data from groups of patients spanning MDD and BD found both agitation/anxiety and retardation factors cutting across BD and MDD depressive episodes [8•]. A study of MDD found that negative affect and agitation factors both predicted neurocognitive impairment, while lassitude and malaise did not, implying that agitation was a core component of depression in MDD [13].

Agitated Depression: MDD or BD?

Prominent agitation during depressive episodes was associated (but not universally) with other characteristics of mixed states and bipolar disorder including early onset, recurrent course, and family history of bipolar disorder [14]. However, motor agitation during depressive episodes was only associated with indicators of a bipolar course of illness when additional manic symptoms were present [15, 16]. The strength of association between psychomotor agitation and diagnosis varies substantially across studies. In a large number of both BD and MDD depressed patients, 76 % of agitated depressive episodes were considered mixed depressions (at least three manic symptoms) compared with 14 % of non-agitated patients. Similarly, individuals diagnosed with MDD (no free-standing manic or hypomanic episodes) who were experiencing depressive episodes with psychomotor agitation had courses of illness resembling BD only if, in addition to psychomotor agitation, at least one additional manic symptom was present [17]. Another study of 314 carefully characterized patients with MDD found that the 19 % with psychomotor agitation had more severe psychotic symptoms than those without agitation, but did not have other symptomatic or illness-course characteristics suggesting BD [18]. These findings suggest strongly that, while agitated depressive episodes are often mixed states, this is far from always the case.

Psychomotor Agitation and Retardation are not Mutually Exclusive

One important characteristic of agitation in depression is that agitation and psychomotor retardation are not mutually exclusive [19] and can be essentially orthogonal in factor analyses [2•, 20]. A person who is barely moving can be experiencing intense inner turmoil and tension. Further, an agitated person may be wringing his hands, pacing the floor, and talking incessantly—but slowly. Angst et al. [21] conducted a valuable longitudinal analysis of this phenomenon as part of the Zurich study. They found that, during depressive episodes, BD was more likely than MDD to be associated with both psychomotor agitation and retardation. Patients experiencing only retardation during depressive episodes were somewhat more likely to have BD—but this was not uniformly the case. Patients experiencing only psychomotor agitation were actually twice as likely to have MDD as BD.

Forms of Agitation Associated with Depression or Mania

The nature of agitation may contribute to some apparent contradictions in interpreting agitated depression. Detailed examination of behavior in patients experiencing depressive episodes of MDD and BD, as well as mania, and mixed states, using combined clinician, observer, and self-ratings, yielded evidence for an agitation factor cutting across both BD and MDD depressions [20]. Further, these studies identified two kinds of agitation in manic, depressive, and mixed episodes [22]. The first, characterized by inner tension, consists of hyperactive thought and behavior that is only weakly goal-oriented, such as pacing, wringing hands, and ruminations. This is characteristic of depressive states and corresponds to Carroll and Klein's "psychic pain" construct [6]. The second, characterized by disinhibited (but generally not well organized) goal-oriented behavior, combined with a lesser degree of inner tension, characterizes manic states. Further, characteristics of inner tension differ between the two models, being in each type of agitation analogous to the nature of increased activity: related to ruminations and anxious misery in

depression-related agitation, and to racing thoughts or flight of ideas in mania-related agitation. Patients in mixed states appear to experience both kinds of agitation [22].

Direct studies of physical activity, using wrist actigraphy, support this model. The transition from depression to mania is associated with increased measured motor activity [23]. However, the volume of physical activity does not correlate significantly with psychomotor agitation, as measured by the Hamilton Depression Rating Scale in MDD [24•]. These results support differentiation of agitation related to increased goal-directed activity and reflected by actigraphy from agitation associated with painful inner tension and not associated with goal-directed activity.

Mixed States

Kraepelin, whose concept of “manic-depressive insanity” combined what we now call MDD and BD, described affective episodes, whether predominately depressive or manic, as combinations of inhibition or activation along three basic dimensions of behavior: mood, thought, and volition [25]. He referred to episodes combining activation and inhibition in different dimensions as mixed states. The predominately depressive mixed states in Kraepelin’s system were depression with “excitement” or with “flight of ideas.” These constructs have been validated in recent clinical studies [26] and occur potentially, but not always, in the context of bipolar disorder [27, 28]. Importantly, Kraepelin’s formulation did not clearly distinguish hyperactivity in terms of goal-directedness and did not clearly differentiate racing thoughts from uncontrolled ruminations.

The emergence of the idea of two different recurrent depressive disorders, one of which occurring in a course combined with manic episodes, altered the status of mixed states. Because they were considered to be combinations of depression and mania, and because mania was defined as specific to BD, mixed states were generally, but not always, considered specific to BD. This raised the related questions of whether agitated depression was a mixed state, and, if so, was perforce a component of BD [11, 29].

Bipolar Depression Versus MDD

The clinical phenomena of BD have been described over centuries, but have only been formally defined in the last 60 years or so as a unitary condition defined by recurrent depressive and/or manic episodes. Compared with MDD, BD is considered to have a more recurrent course with earlier onset, though the illnesses overlap in these characteristics [14]. While BD was once considered to be characterized more by depression with psychomotor retardation, and unipolar disorder by psychomotor agitation, more recent studies have confirmed that in terms of the symptomatic depressive episode *per se*, there are no pathognomonic features of either illness [30, 31], other than co-occurrence of mania in mixed states. According to this view, the pathognomonic syndromal characteristic of BD is mania (broadly defined to encompass hypomania, including brief hypomania), so mixed states would of necessity be part of bipolar disorder.

Some individuals with illness-course and family history strongly suggesting BD appear to experience manic symptoms only while they are depressed (sometimes referred to as pseudo-unipolar, as these patients have no free-standing manic or hypomanic episodes, but have illness-course and treatment response characteristics strongly resembling bipolar disorder) [14, 32]. This has raised the question of whether all agitation is mania, or whether psychomotor agitation can exist independently of mania. The most common intra-depressive episode manic symptoms were irritability, racing thoughts, psychomotor agitation, and increased talkativeness [33]. It is notable that, of these, irritability and psychomotor agitation occur in mania, but also in well-characterized patients, who have apparently never been manic, whose illness courses are not pseudo-unipolar but are actually consistent with MDD rather than BD [22, 34]. Symptoms occurring during depressive episodes in patients with MDD that predicted change of diagnosis to BD due to subsequent free-standing manic or hypomanic episodes included decreased need for sleep, increased energy, and increased goal-directed activity [35••].

Other studies have found similar results within depressive BD episodes. One study found that more than 75 % of BD depressive episodes had subsyndromal manic symptoms [36]. These symptoms were associated with severity of depressive symptoms and of suicidal behavior. The most prevalent symptoms were overt irritability and psychomotor agitation. Similarly, a study of manic symptoms in BD depressive episodes found that, using ROC analysis, SADS Mania Rating Scale scores greater than 6 were associated with characteristics considered to describe mixed states, including increased frequency of recurrence, substance-use disorders, suicidal behavior, and impulsivity [37]. Similar results emerged from a study combining depressive and manic patients, in which severity of the non-predominant affective state predicted these same features in a graded and symmetrical manner, whether starting from purely manic or depressive states [3]. Whether the predominant polarity was depressive or manic, worry, negative self-evaluation, increased energy, visible hyperactivity, and racing thoughts were associated with mixed-state characteristics like recurrent course, early onset, and history of suicide attempt.

Depressive episodes can be similar in BD and MDD, and most episodes of BD, including the first, are usually depressive. Therefore, unless clear mixed features are present, it is usually necessary to look at the course of illness outside of the episode in order to adequately diagnose depressive episodes [38].

What is the Role of Illness-Course Characteristics in Susceptibility to Mixed States?

BD and MDD may differ in illness course and other characteristics that are not part of the depressive syndrome. These include genetics and familiality, age of onset and frequency of recurrence, and susceptibility to behavioral complications, including substance-use disorders, impulsive and/or criminal behavior, and suicidal behavior [14, 39]. Among patients with bipolar depressive episodes, measures of impulsivity, and likelihood of a history of suicidal behavior, increased with increasing mania scores [37] or symptom counts [3]. In groups combining patients diagnosed with BD or MDD, the presence of at least three intra-depressive episode manic symptoms was associated with early onset, frequent recurrence, and positive family history for BD [32]. Similarly, early onset of mood disorder, in a mixed sample of MDD (n=189) and BD (n=245) outpatients, was associated with frequent recurrence, and positive family history for BD [40]. Presence of hypomanic symptoms, especially increased goal-directed activity, increased energy, and decreased need for sleep, confined to major depressive episodes predicts eventual diagnostic change to BD because of emergence of free-standing predominately manic or hypomanic episodes [35••].

In addition to a recurrent episodic course, inter-episode personality characteristics may identify individuals who are susceptible to the abnormal arousal states associated with activated depression. For example, Perugi et al. [41•] identified a relationship between cyclothymic temperament and susceptibility to mixed states. Similarly, increased inter-episode impulsivity is associated with susceptibility to mixed states and their complications [3].

Definitions of Mixed States or Mixed Features: Emergence of a Continuum of Mixed States

Recent studies of mixed states, whether predominately depressive or manic, suggest that there is a continuum from "pure" depressive or manic syndromes, to predominately depressive or manic states with a few features of the other, to the simultaneous presence of full depressive and manic syndromes (reviewed in [7••]). Further, so-called mixed features can emerge during an ongoing episode, whether due to underlying illness characteristics, environmental influences, or pharmacology (prescribed or non-prescribed). Addressing the question of whether a continuum of manic symptoms during depressive episodes represented a continuum between BD and MDD, Benazzi [42] found mixed evidence. Severity of manic symptoms was distributed continuously and unimodally across depressive episodes in a large group comprising both BD and MDD. However, other characteristics, like family history and age of onset, more clearly distinguished two apparently different groups. In a large, multinational sample of MDD and BD depression, patients were classified based on 5 "mania spectrum" and six "depression spectrum" factors [43•]. Severity of psychomotor agitation factor was related to the probability of BD. The factor was broad, combining thought acceleration, distractibility, hyperactivity, and restlessness. Classification was improved by addition of "mixed instability" and suicidal behavior to the model.

Clinical Criteria for Mixed States

Several lines of evidence converge on a clinically useful definition of mixed states requiring a depressive or manic episode with at least three symptoms of opposite polarity [7••]. The evidence arises both from studies combining bipolar and major depressive disorders [44] and from studies within bipolar disorder [3]. This formulation is based on mounting evidence that, in either depressive or manic episodes, as the number of symptoms, or rating scale scores, for the opposite polarity increase, certain characteristics emerge, generally including early onset, history of trauma, frequent recurrence, history of suicidal behavior, substance-use disorder, susceptibility to anxiety and psychosis, and family history of bipolar disorder [7••]. Detection of mixed states can be difficult, as the symptoms of the predominant polarity can be more intense than the mixed symptoms are [45•].

Mechanisms and Consequences of Activated Depressions

Non-Affective Symptoms Related to Activated Depression

Increased arousal is a highly salient feature of activated depressions, whether they are characterized as mixed states or as agitated depression [46]. Bertschy et al. [47] developed a construct of dysphoria, which consisted of at least three of inner tension, irritability, aggressive behavior, and hostility. Dysphoria was present in 18 % of patients with "pure depression." Twenty-three percent of those had "pure mania," and 73 % of those had "full mixed" states. Henry et al. [48] developed a comprehensive behavioral measurement scale that detected emotional hyper-reactivity as a central component of apparent mixed states. This should be explored further as a potential differentiator of depressive MDD and BD episodes.

Treatment Considerations

The definition of agitation in agitated depression implied a combination of outward hyperactivity and inner tension [10]. These episodes were generally treated with antipsychotic, as well as antidepressive, agents [17]. Among antidepressive agents, those acting mostly as serotonin reuptake blockers, originally tertiary amine tricyclics, were once considered the most effective. More recent findings suggesting that depressive episodes, perhaps especially agitated depressive,

include mixed states that might be worsened by conventional antidepressive agents, increase the urgency of identifying depressed patients for whom conventional antidepressants should not be used—at least as monotherapy [11, 14, 17]. Even adjunctive antidepressant use was associated with increased severity of mania without favorable effect on depressive symptoms [49].

A comprehensive review of antidepressant-induced affective state change relative to diagnostic shift from MDD to BD revealed that the rate of switch from depression to hypomania was more than five times that of diagnostic change to BD [50•]. One might expect the two rates to be equal. The authors pointed out that it is impossible to distinguish the extents of switching due to unrecognized BD versus "mood-elevating pharmacological effects" of antidepressants (to which one would expect BD to confer greater susceptibility).

Biological Comparisons Between Mixed States and Agitated Depressions

Some Neurobiological Correlates of Agitated Depression

Depressive states appear to be associated with hypothalamic-pituitary-adrenocortical (HPA) axis activation [51]. HPA activation is related to psychomotor agitation and anxiety in both BD and MDD [52]. Sympathoadrenomedullary function is also increased in a manner that correlates with severity of anxiety and agitation in MDD or BD depressed patients without manic symptoms [53], and in mixed, but not non-mixed, mania [54]. This observation suggests that increased epinephrine and metanephrine excretion (evidence of adrenomedullary activation) are consistent with increased "depressive" agitation across MDD and BD depressive states, whether mixed or non-mixed. These aspects of psychomotor agitation appear to go across MDD and BD, and could be construed as evidence for a single illness. However, identical psychomotor manifestations of BD and MDD depressions had contrasting relationships to measures of neurotransmitter function [55].

Neurobiological Correlates of Mixed States

There are relatively few neurobiological studies of mixed states. Existing findings favor the model of superimposed activating and depressive phenomena, at least on the surface, providing less information about what might be driving these states. In the absence of depressive symptoms, mania is associated with catecholaminergic activation [56], but not with prominent HPA over-activity [57]. Patients in mixed manic states have HPA activation that resembles or exceeds that in agitated depression (and correlates with depressive symptom ratings [57]), combined with catecholamine activation exceeding that in nonmixed mania [58]. This resembles characteristics of individuals essentially stuck in a transition between manic and depressive states [59, 60].

Impulsivity and Suicidal Behavior in Activated Depressions

Impulsivity is increased in BD and MDD [61]. Impulsivity appears to be related, in a graded manner, to the presence of mixed features in either depressive [37] or combined depressive and manic [3] episodes. Consistent with this relationship to mixed states and to arousal, impulsivity is also strongly related to anxiety across a range of conditions [62, 63].

Activated depression carries a risk for potentially harmful behavior, including suicidality [39, 64], regardless of diagnosis [65]. This may be increased by the prominent aggressive/hostile aspects of dysphoria [47].

A study of 4,441 patients followed over 35 years found 96 completed suicides [66••]. Patients committing suicide were more likely to have bipolar disorder than other diagnoses. The commonest symptoms in suicide completers, in order, were inner tension, racing thoughts, aggressive behavior, guilt, and psychomotor agitation. Brief or no mood-stabilizer treatment, and prolonged antidepressive treatment, were also associated with increased likelihood of suicide.

More extensive data link attempted suicide to activated depression, reporting increased likelihood of suicide with

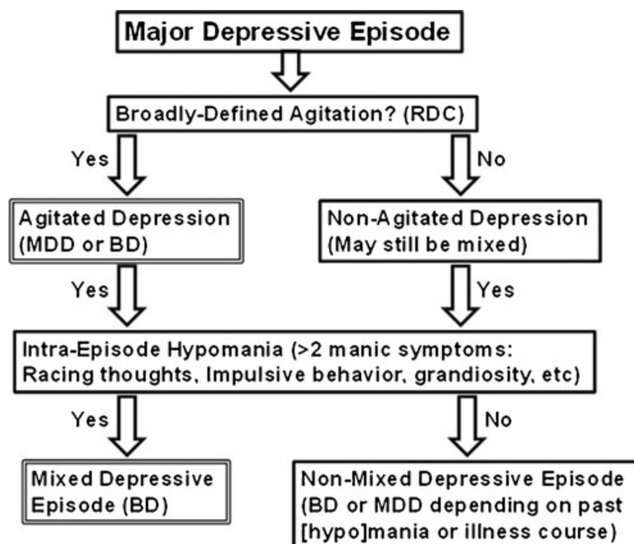

Fig. 1 Identifying and characterizing activated depressions. Summary of material discussed in this article to provide a flow chart for identification of activated depression. Once activated depression is recognized, the clinician must determine whether mixed features, beyond nonspecific tension and motor agitation, are present. Whether or not an episode is mixed, it is necessary to characterize history of hypomanic or manic episodes and of other illness-course characteristics, including family history, age of onset, frequency of recurrence, and previous responses to treatment

higher numbers of mixed symptoms [14, 64, 67] or scores for mania ratings among depressed patients [37] or scores for opposite-polarity ratings across manic and depressed patients [3]. As antidepressive treatments can increase activation in BD depressive episodes and can trigger mixed states [68], differentiating BD from MDD depression is vital in choosing treatment [69]. Similarly, risk for suicidal behavior in bipolar disorder was related to impulsivity during [37] and independent of [70] depressive episodes.

Conclusions

Activated depression is an important and potentially dangerous clinical entity. Figure 1 summarizes salient characteristics that are involved in identifying and characterizing activated depressive episodes. For reasons of acute treatment and long-term strategy, it is necessary to determine whether the activated depressive state is related to MDD or BD. As reviewed here, the preponderance of evidence suggests that either could be the case. Most, but not all, mixed states can be considered as agitated depression—and many, but not all, agitated depressions can be considered as mixed states. Extra-episode characteristics, like course of illness, may be decisive factors in determining whether an episode is part of BD, regardless of activation. As clinicians, we must be alert to characteristics of activated depression, to its possible relationship to BD, and to the fact that activation may emerge during on ongoing depressive episode of either BD or MDD.

Compliance with Ethics Guidelines

Conflict of Interest Alan C. Swann declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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