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Research Article

Revisiting Mixed Depression: Toward a Bidimensional Model of Expansive and Excitative Activation

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Abstract

Mixed depressive states remain difficult to define because clinically meaningful activation during depression is heterogeneous and is not fully represented by existing diagnostic frameworks. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) mixed-features specifier identifies a restricted set of manic-spectrum symptoms in the context of a depressive episode, while symptoms such as psychomotor agitation and irritability are excluded from the specifier on the basis of their conceptual overlap with depressive symptoms. Alternative clinical and research traditions, particularly those concerning agitated or mixed depression, have instead emphasised inner tension, restlessness, irritability and psychomotor activation.

This Perspective proposes a bidimensional conceptual model comprising two potentially distinguishable but frequently overlapping forms of activation during depression: expansive activation and excitative activation. Expansive activation refers primarily to outwardly expressed activation with features suggestive of bipolar-spectrum phenomenology, such as elevated or expansive mood, self-inflation, behavioural disinhibition and increased goal-directed activity. Excitative activation refers primarily to internally experienced or agitated activation, including inner tension, psychomotor agitation, irritability, anxiety and restlessness. The Shahin Mixed Depression Scale (SMDS), which has demonstrated psychometric validity for non-Diagnostic and Statistical Manual of Mental Disorders (non-DSM) mixed features associated with agitation and inner activation, provides an empirical foundation for the excitative dimension.

The proposed framework is deliberately presented as hypothesis-generating rather than as an established diagnostic classification. Preliminary operational criteria are proposed, including a threshold of three or more activation symptoms and the presence of activation during the majority of days of the current depressive episode, while recognising that optimal thresholds and duration requirements require prospective validation. The framework is intended to generate testable hypotheses concerning phenomenology, bipolarity, treatment response and longitudinal course. A structured pilot programme is proposed as the next step toward determining whether the two dimensions can be reliably distinguished and whether they provide clinically meaningful information beyond existing diagnostic systems.

Keywords: Mixed depression, Mixed features, Bipolar spectrum, Activation, Agitation, Dimensional psychopathology; Shahin Mixed Depression Scale

Introduction

The coexistence of depressive and activated phenomena has been recognised since the classical descriptions of manic-depressive illness. Kraepelin described a range of mixed states in which depressive affect could coexist with excitation, activation or other manic phenomena [1]. Subsequent clinical traditions continued to describe depressive states accompanied by psychomotor agitation, inner tension, racing thoughts and irritability.

Modern diagnostic systems have approached these presentations differently. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) replaced the former mixed-episode category with a mixed-features

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specifier. In depressive episodes, the specifier is based primarily on symptoms derived from the manic/hypomanic domain, while symptoms considered overlapping between depression and mania – including irritability, distractibility and psychomotor agitation – are not counted toward the specifier. This approach provides operational reliability but leaves clinically important forms of activated depression outside the formal specifier.

The problem is not merely semantic. Several clinical and research traditions have independently described depressive states characterised by marked activation without the full phenomenology of mania or hypomania. Koukopoulos and colleagues conceptualised agitated depression as a mixed state, emphasising inner psychic tension, psychomotor agitation and racing or crowded thoughts [2]. Perugi and colleagues subsequently described depressive mixed states in bipolar illness that were clinically distinguishable from retarded depressive states [4]. Other work has demonstrated that manic-spectrum symptoms occurring during major depressive episodes may identify a clinically meaningful bipolar-spectrum subgroup [7].

The resulting literature therefore contains more than one form of activation during depression. One group of symptoms is predominantly outwardly expressed and resembles the phenomenology of hypomania or mania; another is characterised predominantly by inner tension, agitation, irritability and restlessness. Whether these represent separate dimensions, overlapping manifestations of a common process, or different points on a single continuum remains an empirical question.

This Perspective proposes a framework intended to make that question testable.

Background and Rationale

Historical and phenomenological basis

The concept of mixed depression has never been restricted to euphoric or classically manic symptoms. Historical descriptions and subsequent clinical work have repeatedly identified depressive states accompanied by psychic agitation, restlessness, irritability and increased motor activity [2].

Koukopoulos and colleagues specifically argued that agitated depression could represent a mixed state and proposed criteria incorporating psychomotor agitation, psychic agitation or intense inner tension, and racing or crowded thoughts [2,3]. A subsequent study by Benazzi, Koukopoulos and Akiskal examined an operational definition of agitated mixed depression in patients with major depressive episodes and found associations with bipolar II disorder and other bipolar-spectrum validators [8].

The Clinical Research Diagnostic Criteria for Bipolar Illness (CRDC-BP) proposal is particularly relevant because it explicitly recognises that mixed depression has been conceptualised in different ways and proposes that competing definitions should be subjected to empirical validation rather than prematurely assuming that one definition is definitive [9].

Thus, the current literature provides a rationale for asking whether activation during depression should be differentiated phenomenologically rather than treated as a single undifferentiated construct.

Bidimensional Model of Activation

The proposed model distinguishes two dimensions:

- **Expansive Activation:** Expansive activation is characterised predominantly by outward-directed activation and features that may indicate bipolar-spectrum involvement: elevated or expansive mood; self-inflated or grandiose self-appraisal; behavioural disinhibition; increased goal-directed activity; and increased or pressured activity or speech. The central phenomenological feature is externalised activation with an expansive or self-enhancing quality. This dimension is conceptually related to manic or hypomanic phenomenology, but its presence during a depressive episode would not, by itself, establish a diagnosis of bipolar disorder.
- **Excitative Activation:** Excitative activation is characterised predominantly by internal or agitated activation, including: inner tension; psychomotor agitation; irritability; anxiety or marked restlessness; and subjective psychic activation. This dimension has a stronger historical relationship with the literature on agitated and mixed depression. Importantly, the model does not assume that excitative activation is synonymous with bipolarity. Rather, it is proposed as a clinically relevant activation dimension that may occur across diagnostic backgrounds.

Why Two Dimensions?

The distinction is based primarily on phenomenological differences, not on an assumption that two biological mechanisms have already been demonstrated.

Existing research provides partial support for the separability of relevant symptom clusters. The Shahin Mixed Depression Scale (SMDS) study, for example, identified a two-factor structure involving psychomotor agitation and mixed symptoms without psychomotor agitation [5]. This finding does not establish the proposed expansive–excitative model, but it demonstrates that activation-related symptoms in depression can show more than one psychometric pattern.

Similarly, research on depressive mixed states has identified clinically distinguishable presentations involving agitation and manic-spectrum symptoms [4,8]. Accordingly, the present model should be regarded as a testable extension of existing phenomenological and psychometric observations, rather than as an established two-factor structure.

Conceptual Framework and Operationalisation

The use of the terms “bipolar-expansive” and “unspecific-excitative” is therefore proposed as a working phenomenological

Table 1: Proposed Clinical Representation

Dimension	*Core Phenomenology*	*Proposed Clinical Representation*	*Current Empirical Status*
Expansive activation	Outward activation, expansive/self-enhancing mood, disinhibition, increased goal-directed activity	Shahin Activated Depression Screener (SADS)	Under development; not yet validated
Excitative activation	Inner tension, agitation, irritability, restlessness/anxiety	Shahin Mixed Depression Scale (SMDS)	Previously psychometrically evaluated
Combined activation	Meaningful features from both dimensions	Future integrated assessment	Requires empirical definition

distinction rather than a formal diagnostic classification.

Proposed Symptom Threshold

For research purposes, the following preliminary thresholds are proposed:

- **Expansive activation:** Presence of ≥ 3 expansive activation symptoms.
- **Excitative activation:** Presence of ≥ 3 excitative activation symptoms.
- **Combined activation:** Presence of ≥ 3 activation symptoms in total across the two dimensions, with clinically meaningful representation of either or both dimensions.

These thresholds are provisional. They are not claimed to have been validated for the proposed bidimensional model. The rationale for using a three-symptom threshold is partly consistent with existing mixed-feature research, including approaches that have operationalised mixed depression using three or more manic symptoms [6,7], while other agitated-depression approaches have used different thresholds [2]. The variation itself supports the need for empirical determination of the optimal threshold rather than assuming that any single cutoff is definitive.

Duration

A second provisional criterion concerns temporal persistence. The proposed model requires that activation:

- Be present for at least 2 days, and
- Occur during the majority of days of the current depressive episode.

The two conditions serve different purposes. The first permits identification of clinically meaningful short-lived activation that might otherwise be missed by longer duration requirements. The second preserves the requirement that the activation be a genuine characteristic of the depressive episode rather than an isolated symptom occurring incidentally.

This is explicitly proposed as a research hypothesis, not as a claim that the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) or the Clinical Research Diagnostic Criteria for Bipolar Illness (CRDC-BP) currently uses this exact combined duration rule. The Clinical Research Diagnostic Criteria for Bipolar Illness (CRDC-BP) itself presents alternative research definitions of mixed depression and emphasises that such definitions remain subject to empirical validation [9].

Evidence Base and Methodological Approach

Because this article is a Perspective rather than an original empirical study, no new participants were recruited and no new patient-level data were analysed.

The conceptual model was developed through a narrative synthesis of:

- Classical descriptions of mixed affective states;
- Contemporary literature on mixed and agitated depression;
- Research examining bipolar-spectrum features during depressive episodes;
- Psychometric work concerning non-Diagnostic and Statistical Manual of Mental Disorders (non-DSM) mixed features;
- Research-based nosological proposals, particularly the Clinical Research Diagnostic Criteria for Bipolar Illness (CRDC-BP).

Shahin Mixed Depression Scale (SMDS)

The Shahin Mixed Depression Scale (SMDS) is the principal existing psychometric instrument relevant to the proposed excitative dimension. In its validation study, 170 patients with unipolar depression underwent assessment using the Shahin Mixed Depression Scale (SMDS) and expert interviews based on established mixed-depression criteria [5]. The scale demonstrated good internal consistency and high sensitivity and specificity against the study's reference standard. Factor analysis identified one factor related to psychomotor agitation and another involving mixed symptoms without psychomotor agitation [5].

These findings provide empirical support for the clinical relevance and measurable nature of non-Diagnostic and Statistical Manual of Mental Disorders (non-DSM) activation in depression. They do not, however, validate the proposed expansive–excitative bidimensional structure. That distinction is important and is explicitly maintained in the present Perspective.

Shahin Activated Depression Screener (SADS)

The Shahin Activated Depression Screener (SADS) is proposed as a future instrument for assessing the expansive dimension. It remains under development and has not yet undergone psychometric validation. It should therefore not

be used as an established diagnostic instrument at this stage.

The next step should be pilot testing against structured clinical interviews and established measures of manic/hypomanic symptoms, bipolarity and depressive severity.

Relationship to Existing Diagnostic Frameworks

The proposed model is not intended to replace Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) or International Classification of Diseases, 11th Revision (ICD-11) diagnostic criteria. Rather, it addresses a different question: What forms of activation are present within a depressive episode, and can their phenomenological differences provide clinically meaningful information?

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) provides a categorical diagnostic framework, whereas the present proposal is dimensional and hypothesis-generating. The Clinical Research Diagnostic Criteria for Bipolar Illness (CRDC-BP) is particularly compatible with this approach because its authors explicitly describe multiple competing definitions of mixed depression and state that empirical research should determine which definitions are valid [9].

The proposed framework therefore extends the research question rather than claiming to have resolved it.

Clinical Correlates and Testable Hypotheses

The model generates several hypotheses that can be tested prospectively.

Expansive activation may be associated with:

- Greater expression of bipolar-spectrum features;
- Hyperthymic or other activation-related temperamental characteristics;
- Behavioural disinhibition;
- Antidepressant-associated switching or activation in susceptible patients.

Excitative activation may be associated with:

- Greater psychomotor agitation;
- Inner tension and anxiety;
- Irritability;
- Suicidal ideation or behaviour in some clinical populations;
- Poorer tolerability of antidepressant treatment in selected activated patients.

These statements are hypotheses rather than established subtype-specific findings. Existing studies provide supporting observations for some individual associations, particularly for agitated depression and bipolar-spectrum mixed states [2,4,8], but do not yet establish the complete proposed profile of either dimension. This distinction is crucial because the current evidence does not justify presenting the two proposed dimensions as biologically or prognostically validated subtypes.

Clinical Implications

The principal potential clinical value of the model is recognition rather than automatic diagnostic relabelling. Identifying activation within depression may prompt clinicians to reassess: lifetime hypomanic or manic symptoms; family history of bipolar illness; previous antidepressant-associated activation; suicidal risk; degree and nature of psychomotor activation; and longitudinal course.

For patients with clear bipolar-spectrum illness, antidepressant monotherapy warrants particular caution. In one observational study of patients subsequently diagnosed with bipolar disorder, initial antidepressant monotherapy was associated with more switching and suicide attempts than treatment combining an antidepressant with an antimanic agent [10], although the study was limited by its small sample and observational design.

Similarly, the literature on agitated depression has raised concerns regarding worsening agitation and other adverse clinical outcomes in some activated depressive patients treated with antidepressants [2]. Accordingly, the present model supports careful reassessment before antidepressant monotherapy in patients with prominent activation, rather than a blanket recommendation against antidepressants in every patient meeting a proposed activation criterion.

Potential Opportunities

The proposed framework could generate several research opportunities:

- **Phenotypic refinement:** Separating expansive and excitative activation may permit more precise description of heterogeneous depressive presentations.
- **Improved psychometric research:** The model provides a framework for testing whether symptoms cluster reproducibly into expansive and excitative dimensions.
- **Longitudinal research:** Repeated assessment could determine whether an individual's activation profile remains stable or changes across depressive episodes.
- **Bipolar-spectrum research:** The expansive dimension could be tested against established bipolar-spectrum validators, while the excitative dimension could be examined independently rather than automatically equated with bipolarity.
- **Treatment research:** Future studies could examine whether the two activation profiles differ in response, tolerability or risk during different treatment strategies.

Potential Challenges

Several challenges must be addressed before the proposed framework can be considered clinically validated:

- First, the two dimensions may not be truly independent. A patient may simultaneously experience expansive and excitative activation.
- Second, some symptoms may be difficult to classify uniquely. Irritability, for example, may occur in depressive, anxious, mixed and manic states.
- Third, symptom thresholds may vary across populations and cultures.
- Fourth, the proposed expansive dimension could overlap substantially with established hypomanic symptoms, raising the question of whether it adds information

beyond existing bipolar-spectrum assessments.

- Fifth, the excitative dimension may occur in anxiety disorders, akathisia, substance-related states and other conditions. Therefore, excitative activation cannot automatically be interpreted as evidence of bipolarity.
- Finally, treatment implications cannot be inferred from the proposed classification until prospective outcome studies are performed.

Proposed Pilot Study

In response to the need for empirical testing, the following staged validation pathway is proposed:

- **Phase 1: Content and construct validation:** Experts in mood disorders would independently rate candidate expansive and excitative symptoms for relevance, clarity, specificity, redundancy, and phenomenological distinctiveness.
- **Phase 2: Pilot clinical study:** Patients presenting with depressive episodes would undergo structured diagnostic assessment, assessment of depressive severity, assessment of manic/hypomanic symptoms, assessment using the Shahin Mixed Depression Scale (SMDS), administration of the preliminary Shahin Activated Depression Screener (SADS), assessment of anxiety, agitation and suicidality, and assessment of lifetime bipolar-spectrum validators. The primary objective would be to determine whether the proposed dimensions can be reliably identified.
- **Phase 3: Psychometric validation:** Future studies should examine factor structure, internal consistency, test–retest reliability, convergent validity, discriminant validity, sensitivity and specificity, and measurement invariance across relevant populations.
- **Phase 4: Longitudinal validation:** Only after initial psychometric validation should the model be examined prospectively for its ability to predict subsequent hypomanic or manic episodes, recurrence, treatment response, treatment-emergent activation, and suicidal outcomes.

Limitations

This proposal has several important limitations:

- The bidimensional model itself has not yet been empirically validated.
- The proposed symptom thresholds and duration criteria are provisional.
- The Shahin Mixed Depression Scale (SMDS) provides empirical support for the measurement of non-Diagnostic and Statistical Manual of Mental Disorders (non-DSM) mixed features but was not designed to validate the complete expansive–excitative model.
- The Shahin Activated Depression Screener (SADS) remains under development and has not yet undergone psychometric evaluation.
- The available literature uses heterogeneous definitions of mixed depression, making direct comparisons difficult.
- The proposed distinction may ultimately prove unnecessary if future factor-analytic or longitudinal studies demonstrate a single underlying activation dimension.
- Biological mechanisms cannot presently be assigned to either dimension. Claims of distinct neurotransmitter, inflammatory or neurobiological mechanisms would therefore be premature.

Conclusion

Mixed depression encompasses heterogeneous forms of activation that may not be adequately represented by a single symptom cluster.

This Perspective proposes a bidimensional, phenomenologically based framework distinguishing expansive and excitative activation during depressive episodes. The model builds on classical descriptions of mixed depression, contemporary research on agitated and bipolar-spectrum depression, the empirical work underlying the Shahin Mixed Depression Scale (SMDS), and research-based nosological approaches such as the Clinical Research Diagnostic Criteria for Bipolar Illness (CRDC-BP).

The proposed dimensions and operational thresholds should not yet be regarded as established diagnostic entities. Their principal value at this stage is to provide a testable framework for prospective psychometric, clinical and longitudinal research.

The central empirical question is therefore not whether the proposed model should replace current diagnostic systems, but whether distinguishing expansive from excitative activation provides information that is reproducible, clinically meaningful and incrementally valid beyond existing measures of depression and bipolarity.

Declarations

- **Ethics approval and consent to participate:** Not applicable as this is a theoretical Perspective article and narrative synthesis of existing literature without human participant recruitment or data collection.
- **Consent for publication:** Not applicable.
- **Availability of data and materials:** Data sharing is not applicable to this article as no new datasets were generated or analysed during the current study.
- **Competing interests:** The author declares that there is no conflict of interest regarding the publication of this paper.
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- **Author contributions:** Islam Shahin conceived, drafted, and revised the manuscript.

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