

Mixed states and suicidal behavior: a systematic review

Estados mistos e comportamento suicida: uma revisão sistemática

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Abstract

Introduction: The objective of this study was to identify whether mixed states in bipolar disorder (BD) are associated with more frequent suicidal behavior when compared to manic/hypomanic and depressive episodes.

Method: We performed a systematic search of the scientific literature on the subject using the PubMed, ISI Web Of Science, PsycINFO and SciELO databases. The terms chosen for the search were (bipolar) AND (suicid*) AND (mixed). We selected original studies comparing suicidal behavior of patients in mixed states and suicidal behavior of patients in other BD phases.

Results: Sixteen papers fit the selection criteria. Twelve of the original 16 studies compared suicidal behavior in mixed states and pure mania, and the majority of these studies (n = 11) revealed that suicidal behavior was more frequent among individuals in mixed states. Five of the papers compared suicidal behavior between depressive and mixed phases of BD. One of these five papers reported more severe suicidal behavior in patients in mixed states and another described more frequent suicidal behavior in patients with pure depression. There were no significant statistical differences between groups in the remaining three of these five studies.

Conclusion: During acute BD episodes, suicidal behavior is more strongly associated with mixed states than with pure mania or hypomania. However, it was not possible to demonstrate that the association between suicidal behavior and mixed states is stronger than the association between suicidal behavior and depressive phases. The results hereby presented are worth considering in clinical practice to better evaluate suicide risk and to prevent suicide.

Keywords: Bipolar disorder, suicide, systematic review.

Resumo

Introdução: Identificar se, no transtorno bipolar (TB), os estados mistos estão associados a um maior comportamento suicida, quando comparados a episódios maníacos/hipomaníacos e depressivos.

Método: Realizamos uma busca sistemática da literatura científica utilizando as bases de dados Pubmed, ISI Web of Science, PsycINFO e SciELO com os termos (bipolar) AND (suicid*) AND (mixed). Foram selecionados estudos originais que compararam o comportamento suicida entre pacientes em estado misto e pacientes em outras fases do TB.

Resultados: 16 artigos se adequaram aos critérios de seleção. Doze desses 16 estudos compararam estado misto com mania pura, e a maioria desses 12 estudos (n = 11) mostrou que o comportamento suicida era mais frequente entre os indivíduos em estado misto. Somente cinco dos artigos incluídos compararam o comportamento suicida entre as fases depressiva e mista do TB. Dentre esses cinco artigos, um mostrou maior comportamento suicida nos pacientes em estado misto, e um mostrou maior comportamento suicida nos pacientes com depressão pura. Em três desses cinco estudos, não houve diferença estatisticamente significativa entre os grupos.

Conclusão: Durante um episódio agudo do TB, os estados mistos estão mais relacionados ao comportamento suicida do que os episódios de mania ou hipomania puros. Todavia, não foi possível demonstrar que os estados mistos cursem com um maior risco de comportamento suicida do que os episódios depressivos puros. Os resultados aqui apresentados merecem ser considerados na prática clínica, a fim de avaliar melhor o risco de suicídio, bem como prevenir o suicídio.

Descritores: Transtorno bipolar, suicídio, revisão sistemática.

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Introduction

Bipolar disorder (BD) is one of the most severe mental disorders. It is characterized by marked mood swings, changes in psychomotor activity, recurring and chronic course, and high level of impairment.¹ Mixed states are complex presentations of BD and consist of a clinical condition in which manic and depressive symptoms are present simultaneously.²

From Heinroth's hypo-asthenia in 1918 until the advent of the Diagnostic and Statistical Manuals of Mental Disorders (DSM), the concept of mixed states has varied considerably and has had diverse definitions.³ In 1992, McElroy et al.⁴ proposed the Cincinnati criteria to conceptualize "mixed mania." According to them, a mixed mania episode would consist of a manic or hypomanic episode followed by three or more depressive symptoms ("defined mixed mania"). However, if only two depressive symptoms were present, a "probable mixed mania" should be diagnosed. Years later, Cassidy et al.⁵ coined a less restrictive definition of mixed mania, which would be based on a threshold of symptoms established by Receiver Operating Characteristic analysis (ROC-derived).⁶ According to this definition, only two of six depressive symptoms (depressed mood, anhedonia, guilt, suicidal behavior, fatigue, and anxiety) together with a manic episode are needed to characterize "mixed mania."

Perugi et al.⁷ created the alternative Pisa criteria. According to them, a mixed state consists of a state of sustained emotional instability and/or perplexity experienced for at least two weeks, in which manic and depressive symptoms are simultaneously present in a fluctuating manner. Opposite extreme manifestations in at least two of the five following areas should be present at the same time: mood (sad-anxious vs. euphoric-irritable), thought flow (slowing vs. racing), thought content (depressive vs. expansive), perceptual disturbance (depressive vs. expansive) and motility (retardation vs. acceleration). A few years later, Akiskal and Bennazi⁸⁻¹² worked on the conceptualization of "depressive mixed state", which they defined as an episode of major depression associated with three or more hypomanic symptoms.

The definitions of mixed states proposed in the DSM-III, DSM-III-R, DSM-IV, and DSM-IV-TR required concomitance of one major depression episode and one complete manic episode. In contrast, the newest edition of the American Statistical Manual, DSM-5, excluded the expression "mixed state" and created mixed-features specifiers for manic, hypomanic, or depressive episodes, if they occur concomitantly with three or more symptoms of the opposite pole. This

decision was made in order to better account for the highly prevalent subsyndromal presentations that did not meet the criteria for any of the bipolar diagnoses in DSM-IV-TR.¹³

Individuals with mental disorders have higher rates of suicide when compared with the general population, and one of the highest rates of suicide is found among patients with BD – approximately 164 per 100,000 person-years.^{14,15} Moreover, suicide attempts are much more lethal in BD, completed in one in every 3 or 4 attempts, whereas in the general population suicide occurs in one in every 30 attempts.¹⁶

A few studies suggest that suicidal behavior in BD varies according to its phases. It would be expected to be more frequent during depressive and mixed episodes and less frequent in manic and hypomanic phases.¹⁷ In mixed states, the hopelessness of depression may be compounded by the hyperactivity and impulsivity of mania, creating a dangerous combination that makes affected individuals more vulnerable to suicidal behavior.¹⁸

This study is a systematic review that aims to identify whether mixed states in BD are more strongly associated with suicidal behavior when compared with other phases of the disorder. To achieve this, we searched for studies comparing suicidal behavior of BD patients in mixed states and suicidal behavior of BD patients in mania or a depressive phase. In this review, mixed states were defined according to the criteria chosen by the authors of each selected paper. To the best of our knowledge, no other systematic review about suicidal behavior specifically in mixed BD states has been performed previously.

Method

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹⁹ We performed a systematic review of the scientific literature on the theme up to March 30th, 2018, of articles published at any time before this date. The databases searched were PubMed, ISI Web of Science, PsycINFO, and SciELO, and the terms chosen were (bipolar) AND (suicid*) AND (mixed).

After the initial search, the following criteria were used to select the papers for this study:

- Original clinical studies published in English, Portuguese, Spanish, or French, with no restriction regarding period of publication.
- Studies comparing suicidal behavior between at least two groups of patients with BD and in

different phases of the disease; groups with at least 10 individuals each; one of the groups composed of patients with BD in a mixed state; no restriction regarding age of patients.

- Diagnostic evaluation of BD in papers should be made according to operational criteria.
- Papers should assess suicidal behavior according to specific criteria or objective data.

Mixed states were defined according to the criteria chosen by the authors of each study selected. Suicidal behavior was defined as: suicidal ideation, suicidal attempts, or completed suicide. Suicidal ideation was defined as a range including thoughts of death, thoughts that it would be better to be dead, expression of the desire of dying, and planning suicide. Suicidal attempts were defined as any degree of self-aggression in which the intension was self-annihilation.

Only papers that researched intra-episodic (during the index episode) suicidal behavior were selected. In fact, since this is a cross-sectional evaluation, neither longitudinal prospective results nor papers containing only evaluations of previous suicidal behavior (i.e., lifetime suicidal attempts) were included.

Titles and abstracts were screened independently by the first and second authors of this study in order to eliminate obviously irrelevant publications. The full-texts of potentially relevant articles were further screened for eligibility by both authors. Disagreements were discussed and consensus was reached in all cases. Afterwards, the following data were extracted from the papers selected using a piloted form: year of publication, location of study, study design, samples and their sociodemographic characteristics, evaluation of the mixed state, assessment of suicidal behavior, and the results of the comparison of suicidal behavior between the different phases of BD.

Results

The searches of PubMed, ISI Web of Science, PsycINFO, and SciELO databases initially yielded 1,211 papers. Exclusion of duplicates resulted in 667 remaining records. Of these, 553 papers were excluded based on the title or abstract for the following reasons: 312 were not original studies, 233 did not have a minimum of 10 individuals diagnosed with BD and in mixed state, and 8 were not published in English, Spanish, Portuguese, or French. Next, the full texts of the 114 remaining papers were assessed in order to evaluate their eligibility.

This process led to exclusion of 98 papers for the following reasons: 9 did not have operational criteria to diagnose BD, 31 did not have a group of individuals

diagnosed with BD in non-mixed episodes, and another 58 did not assess intra-episodic suicidal behavior. Finally, the 16 remaining papers were eligible for this review. Figure 1 shows a diagram illustrating our systematic search.

The sixteen clinical studies included in this systematic review have diverse methodologies and different objectives. However, all of them compared intra-episodic suicidal behavior between individuals in mixed states and patients in other phases of BD. The main characteristics of the articles selected are described in Tables 1 and 2.

Mixed state vs. manic episode

Twelve of the 16 articles included in this review compared suicidal behavior of patients in mixed states and patients in pure mania (Table 1).^{5,7,20-29} One of these 12 papers also compared suicidal behavior between patients in mixed states and patients in a pure depressive episode.²⁷

These papers had samples of varying sizes. The largest comprised 1,035 individuals with BD type I (348 in mixed mania and 647 in pure mania) and the smallest comprised 49 individuals diagnosed with BD type I (29 in mixed state and 20 in pure mania).^{20,24} The samples in all of the papers were made up of adults of both sexes.

The papers selected used different criteria to define mixed states. Only 2 of the 12 articles that compared mixed states and pure mania used the DSM-5 criteria.^{20,21} Four papers used the more restrictive criteria from DSM-III, DSM-III-R or DSM-IV.^{7,24,25,28} Two papers defined mixed states according to the Cincinnati criteria, and 2 other papers used a definition derived by ROC analysis.^{5,22,23,26} Spitzer et al.³⁴ decided that patients fulfilling the Research Diagnostic Criteria (RDC) for mania as well as depression would be in "depressive mania."^{27,29} Perugi et al.⁷ elaborated and used criteria that would later be called the Pisa criteria.³²

Six of the twelve papers that compared mixed states and pure mania assessed suicidal behavior through items evaluating suicide from the following scales of clinical evaluation: Scale for Manic State (SMS), Carroll Depression Scale (CDS), Hamilton Depression Rating Scale (HAM-D), and Schedule for Affective Disorders and Schizophrenia (SADS).^{5,22,23,25,27,29,35-37} The 6 remaining papers evaluated the proportion of individuals who had had suicidal ideation or suicidal attempts without using a formal research instrument.^{7,20-22,24,26}

Three of the twelve papers assessed solely the existence of suicidal attempts, three evaluated only the presence of suicidal ideations, and six analyzed both suicidal attempts and suicidal ideations in the index episode.^{5,7,20-29}

In eleven of the twelve papers comparing individuals in mixed states with individuals in pure mania, suicidal behavior was more frequent in the group of patients in mixed states.^{5,7,21,23,25-27,29} Only one of the twelve papers did not show significant statistical difference between groups.²⁴ Specifically, in Shim et al.'s paper²² there was a third group of patients, with "probable mixed mania", characterized by the occurrence of only two depressive symptoms associated with the manic symptoms. No differences between pure mania and "probable mixed mania" were found, but the patients who were in "defined mixed mania" with at least three depressive symptoms had stronger suicidal behavior than those in pure mania.

Mixed state vs. depressive episode

We found only five papers comparing suicidal behavior in patients with BD in a mixed state and patients with BD in a depressive episode (Table 2).^{27,30-33} Only one of them also compared suicidal behavior between patients in mixed state and patients in pure mania.²⁷

The sizes of the samples did not vary much. The largest comprised 154 individuals with BD type I (36 in a depressive episode, 118 in a mixed episode) and the smallest comprised 64 individuals with BD (23 in a pure depressive episode, 41 in a mixed depressive episode).^{32,33} The samples were usually homogeneous and made up of adults of both sexes.

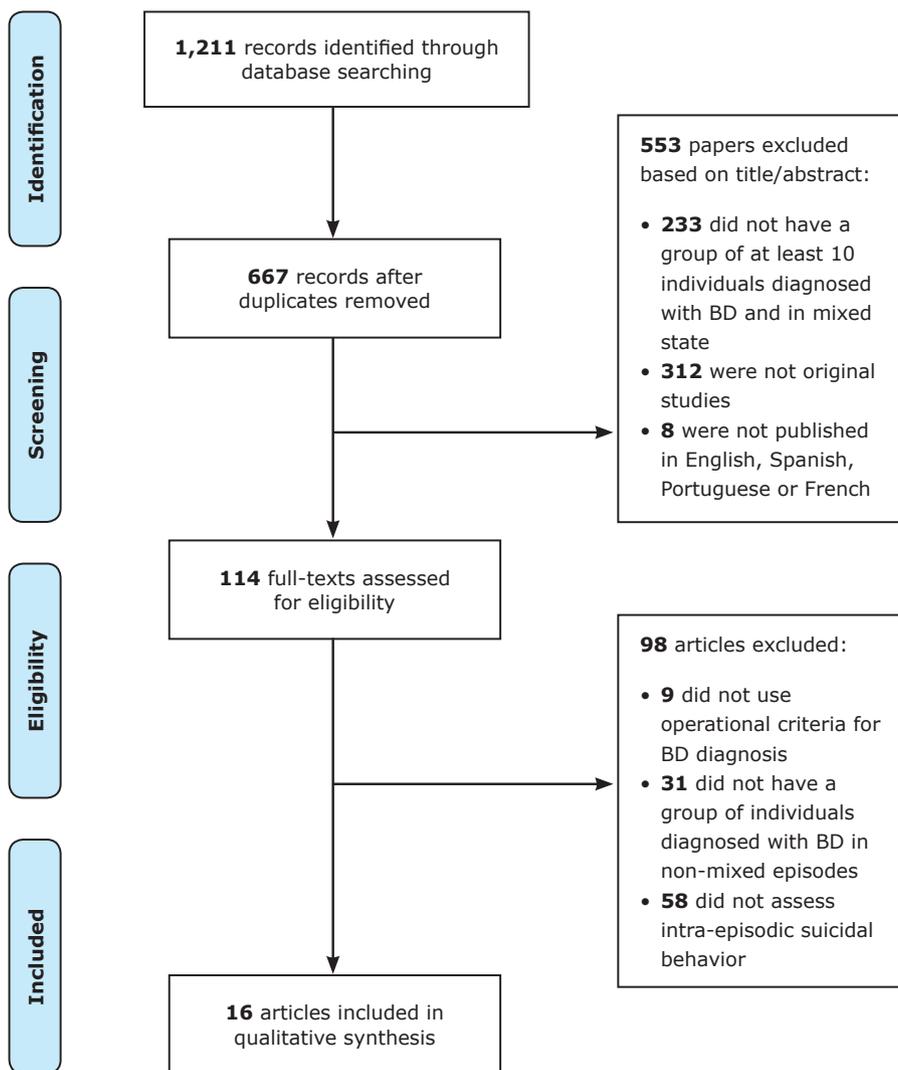


Figure 1 - Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. BD = bipolar disorder.

Table 1 - Studies comparing suicidal behavior between mixed states and manic episodes

Article	Location	Objective	Method	Samples	Sociodemographic factors	Mx evaluation	Assessment of suicidal behavior	Suicidal behavior results
Young ²⁰	Centers in Australia, Brazil, Canada, Germany, Italy, Spain, Turkey, and the UK.	To evaluate BD-I manic patients who met the DSM-5 criteria for BD-I "with mixed features."	The study surveyed psychiatrists and their BD-I manic patients. Data were stratified and characteristics were compared between PM and mMX subgroups.	1,035 BD-I: 348 mMX, 687 PM	Mean age (y): 40; Female gender (%): 52; Employed (%): 44	DSM-5	Number of patients with at least one suicide attempt	mMX (38%) > PM (9%)
Reinares ²¹	Catalonia, Spain.	To compare manic patients with and without mixed features to validate the relevance of the DSM-5 mixed specifier.	Bipolar patients presenting a manic episode were evaluated and systematically assessed for a 6-month period.	169 BD-I: 46 mMX, 123 PM	Mean age (y): mMX = 41.85, PM = 44.35; Female gender (%): mMX = 43.3, MP = 45.7; Married (%): PM = 35.8, mMX = 141.3; Employed (%): PM = 29, mMX = 19	DSM-5	Number of patients with suicidal ideation	mMX (26.1%) > PM (12.3%)
Shim ²²	Seoul, South Korea	To reevaluate the feasibility of diagnosing a bipolar mixed mania and to elucidate the clinical characteristics, treatment response, and course of the illness.	BD-I manic inpatients were divided according to Cincinnati criteria. Charts were reviewed for demographic and clinical characteristics.	171 BD-I: 67 PM, 79 PMX, 25 DMX	Mean age (y): PM = 41.8, PMX = 35.2, DMX = 33.2; Female gender (%): PM = 40.3, PMX = 70.9, DMX = 68; Married (%): PM = 59.7, PMX = 46.8, DMX = 52	Cincinnati criteria	Number of patients with suicidal ideation or with at least one suicide attempt	DMX (28%) > PM (0%); PMX (5.1%) = PM (0%); DMX (28%) > PMX (5.1%)
Cassidy ²³	USA	To examine whether patients' depression self-ratings agree with observer ratings and whether patients rate their depressive symptoms differently during manic and mixed episodes.	Patients' depression self-ratings were compared with observer ratings, as were differences between the manic and mixed subtypes.	94 BD-I: 65 PM, 29 Mmx	Mean age (y): 40.9; Female gender (%): 39.4; Ethnic group (%): Whites: 57.4, Blacks: 42.6	ROC-derived	Mean scores on the suicide items of HAM-D and CDS scales	HAM-D: mMX (0.759) > PM (0); CDS: mMX (0.759) > PM (0.108)
Schwartzmann ²⁴	São Paulo, Brazil	To compare severity between mixed and pure manic episodes.	BD-I mixed and pure manic patients were compared for sociodemographic data and clinical characteristics.	49 BD-I: 29 MX, 20 PM	Mean age (y): PM = 42, MX = 34.8; Female gender (%): MX = 72.4, PM = 80	DSM-IV	Number of patients with at least one suicide attempt	MX (6.9%) = PM (0%)
Cassidy ⁵	Butner, North Carolina, USA	To compare frequencies of the 20 signs and symptoms of SMS between pure and mixed mania. Subtypes were determined by the ROC-derived criteria.	BD inpatients were diagnosed as manic or mixed using the ROC-derived criteria. Frequencies of each sign or symptom of SMS were compared.	363 BD: 280 PM, 83 MX	Mean age (y): 42.1; Female gender (%): 52; Ethnic group (%): Whites: 58.7, Blacks: 40.8, American Indian: 0.3, Asian American: 0.3.	ROC-derived	Number of patients with suicidal ideation according to the SMS suicide item	High threshold (≥ 2 points): MX (31.3%) > PM (0.7%); Low threshold (1 point): MX (49.4%) > PM (4.6%)

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Table 1 (cont.)

Article	Location	Objective	Method	Samples	Sociodemographic factors	Mx evaluation	Assessment of suicidal behavior	Suicidal behavior results
Cassidy ²⁵	Butner, North Carolina, USA	To compare frequencies of the 20 signs and symptoms of SMS between pure and mixed mania. Subtypes were determined with the DSM-III-R.	BD inpatients were diagnosed as manic or mixed using the DSM-III-R criteria. Frequencies of each sign or symptom of SMS were compared.	316 BD-I: 273 PM, 43 MX	Mean age (y): 42.2; Female gender (%): 53.2; Ethnic group (%): Whites: 57, Blacks: 42.4, Oriental: 0.3, American Indian: 0.3	DSM-III-R	Number of patients with suicidal ideation according to the SMS suicide item	High threshold (≥ 2 points): MX (39.5%) > PM (1.8%); Low threshold (1 point): MX (58.8%) > PM (8.8%)
Goldberg ²⁶	New York, USA	To examine suicidality in relation to acute symptom remission in inpatients with mixed and pure BD.	Using chart review, the authors assessed suicidality, other psychopathology, treatment, and remission of BD-I inpatients.	184 BD-I: 77 PM, 107 MX	Mean age (y): 40.4; Female gender (%): 53.8; Ethnic group (%): Whites: 72.3	Cincinnati criteria	Number of patients with suicidal ideation or with at least one suicide attempt	MX (57.9%) > PM (1.3%)
Dilsaver ²⁷	Harris County, Texas, USA	To assess links between suicidality, panic disorder, psychosis, bipolar depression, depressive mania, and pure mania.	BD inpatients in different illness phases were evaluated. Suicidality, intra-episode panic disorder, and psychotic features were ascertained.	129 BD: 53 MDE, 32 MX, 44 PM	Mean age (y): MDE = 34, PM = 33.4, MX = 32.1; Female gender (%): MDE = 64.1, PM = 54.5, MX = 56.3	RDC mania + RDC major depression	Number of patients with a score ≥ 3 in the SADS suicide item	MX (56.3%) > PM (2.3%)
Perugi ⁷	Pisa, Italy	To validate and clinically characterize mixed bipolar states derived from the concepts of Kraepelin and the Vienna School, using the Pisa criteria.	MX patients diagnosed according to Pisa criteria were compared with DSM-III-R PM patients.	261 BD-I: 118 PM, 143 MX	Mean age (y): MX = 37.3, PM = 39.3; Female gender (%): MX = 60.1, PM = 56.8	Pisa criteria	Number of patients with at least one suicide attempt	MX (14.7%) > PM (0%)
Strakowski ²⁸	Cincinnati, Ohio, USA	To determine whether suicidality in mania is associated with increasing depression in general or with the presence of a mixed state per se.	Categorical and dimensional assessments of BD-I inpatients were performed. Mixed and manic bipolar subtypes were compared.	91 BD-I: 57 PM, 34 MX	Mean age (y): 26; Female gender (%): 43; Ethnic group (%): Caucasian: 55, African-American: 40, Not specified: 5	DSM-III-R	Number of patients with a score > 1 in the HAM-D suicide item	MX (26%) > PM (7%)
Dilsaver ²⁹	Houston, Texas, USA	To determine the rate and severity of suicidality among patients with pure and depressive mania.	Severity of current suicidality was compared between patients with pure and depressive mania.	93 BD-I: 49 PM, 44 MX	Mean age (y): PM = 35.2, MX = 32.8; Female gender (%): 61.3; Ethnic group (%): Caucasians: 60.2, African-Americans: 29, Hispanics: 7.5, Not specified: 3.2	RDC mania + RDC major depression	Number of patients with a score ≥ 3 in the SADS suicide item	MX (54.5%) > PM (2%)

BD = bipolar disorder; BD-I = bipolar disorder type I; CDS = Carroll Depression Scale; DMX = defined mixed mania; HAM-D = Hamilton Depression Rating Scale; MDE = pure depressive episode; mMX = mixed mania; MX = mixed state; PM = pure manic episode; PMX = probable mixed mania; SADS = Schedule for Affective Disorders and Schizophrenia; SMS = Scale for Manic State.

Table 2 - Studies comparing suicidal behavior between mixed states and depressive episodes

Article	Location	Objective	Method	Samples	Sociodemographic factors	Mx evaluation	Assessment of suicidal behavior	Suicidal behavior results
Holma ³⁰	Finland	To investigate differences in the risk of suicide attempts between MDD and BD.	Incidence rates for suicide attempts during various illness phases were compared between patients from two different cohorts.	249 MDD, 147 BD; 106 MDE, 41 MX	Mean age (y): MDD = 40.1, MDE = 38.3, MX = 33.6; Female gender(%): MDD = 74.3, BD = 52.8, MX = 63.4; Married (%): MDD = 52.6, MDE = 43.4, MX = 34.1	DSM IV or Benazzi & Akiskal	Suicidal ideation based on SSI score	SSI percentile 50: MX(8) = MDE(5)
Valtonen ³¹	Espoo, Finland	To investigate the differences in prevalence and risk factors for suicidal behavior during different phases of BD.	Suicidal ideation of BD patients was measured. Prevalence and risk factors for suicidal ideation and attempts during different phases were investigated.	144 BD; 15 MX, 24 dMX, 105 MDE	Mean age (y): MDE: 38.4, MX: 36, dMX: 32.4; Female gender (%): MDE: 53.3, MX: 53.3, dMX: 70.8; Married (%): MDE: 42.8, MX: 26.7, dMX: 37.5	DSM IV and Benazzi & Akiskal	Suicidal ideation based on SSI score	SSI percentile 50: MX (12.0) > dMX (6.5) > MDE (5.0)
Perugi ³²	Pisa, Italy	To delineate the clinical profiles of depressive mixed states in the context of BD-I.	The authors studied patients who either met Pisa criteria for bipolar mixed state or DSM-III-R criteria for major depressive episode.	154 BD-I; 118 MX (32 MS-D, 86 MS-DSM), 36 MD-B	Mean age (y): MS-D = 36.3, MS-DSM = 37.7, MD-B = 42.3; Female gender (%): MS-D = 50, MS-DSM = 65.1, MD-B = 52.8; Unemployed (%): MS-D = 12.5, MS-DSM = 8.6, MD-B = 9.4; Married (%): MS-D = 34.4, MS-DSM = 46.5, MD-B = 60	Pisa criteria	Average score on HAM-D suicide item	D-MS (1.04 SD 1.35) = MS-DSM (1.47 SD 1.49) = B-MD (0.73 SD 0.93)
Ciapparelli ³³	Pisa, Italy	To investigate the effectiveness of ECT in medication-nonresponsive patients with mixed mania and bipolar depression.	Patients with mixed mania and bipolar depression assigned for ECT were evaluated the day before starting ECT, 48h after third session, and a week after last session.	64 BD-I; 41 MX, 23 MDE	Mean age (y): MX = 38, MDE = 40.5; Female gender (%): MX = 37, MDE = 39	DSM-IV	Average score on MADRS suicidal ideation item	MX (2.9 SD 1.8) = MDE (3.3 SD 1.5)
Dilsaver ²⁷	Harris County, Texas, USA	To, assess links between suicidality, panic disorder, psychosis, bipolar depression, depressive-manias, and pure-manias.	BD inpatients in different illness phases were evaluated. Suicidality, intra-episode panic disorder, and psychotic features were ascertained.	129 BD: 53 MDE, 32 MX, 44 PM	Mean age (y): MDE = 34, PM = 33.4, MX = 32.1; Female gender (%): MDE = 64.1, PM = 54.5, MX = 56.3	RDC mania + RDC major depression	Number of patients with a score ≥ 3 on the SADS suicide item	MX (56.3%) < MDE (79.3%)

BD = bipolar disorder; BD-I = bipolar disorder type I; dMX = mixed depressive episode; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MD-B = depressive episode by DSM-III-R + does not meet Pisa criteria for mixed state; MDD = major depressive disorder; MDE = pure depressive episode; MS-D = mixed state by Pisa criteria + depressive episode by DSM-III-R; MS-DSM = mixed state by Pisa criteria + mixed state by DSM III-R; MX = mixed state; SSI = Scale for Suicide Ideation.

The definition of a mixed state used in these five papers varied. Ciapparelli et al.³³ adopted the DSM-IV definition. Two papers used Benazzi and Akiskal's⁸ definition and the DSM-IV.^{30,31} Valtonen et al.³¹ created two distinct groups of patients in a mixed state: one with individuals with BD type II in a mixed depressive episode according to Benazzi and Akiskal⁸ and another with patients in a mixed state according

to DSM-IV. In contrast, in Holma et al.'s paper³⁰ there was only one group of patients in a mixed state. It was formed by those who fulfilled the DSM-IV criteria or, alternatively, Benazzi and Akiskal's criteria.⁸ Perugi et al.³² defined mixed states according to the Pisa criteria. Finally, Dilsaver et al.²⁷ defined patients fulfilling RDC for mania as well as for depression as in "depressive mania."

All of the five studies comparing a mixed state with a depressive episode assessed suicidal behavior in a structured manner, using clinical evaluation scales. Two papers assessed suicidal ideation based on the Scale for Suicide Ideation score (SSI).^{30,31,38} Perugi et al.³² and Ciapparelli et al.³³ used the items on suicide in the HAM-D scale and the Montgomery-Asberg Depression Rating Scale (MADRS) respectively.^{36,39} Dilsaver et al. used the item on suicide in SADS. Although all these scales assess suicidal ideation, only HAM-D and SADS also assess suicidal attempts.

One of the above-mentioned five papers showed stronger suicidal behavior in patients in mixed state and one showed statistically significant more frequent suicidal behavior in patients with pure depression.^{27,31} In all the other studies, suicidal behavior was similarly present in the mixed and depressive states in BD.^{30,32,33}

Discussion

This systematic review on suicidal behavior of patients diagnosed with BD has described studies that compared individuals in mixed states with individuals in other phases of the disorder. Our objective was to evaluate whether patients with BD in a mixed state have stronger suicidal behavior than individuals with BD in mania or in a depressive phase.

Patients in mixed states exhibit stronger suicidal behavior when compared with patients in pure mania. Only one of the 12 papers reporting such a comparison that were selected for this review did not show statistically significant differences between groups.²⁴ That article had the smallest sample of BD subjects of all the included studies that compared mixed states and mania, with only 29 patients in mixed states and 20 patients in a pure manic episode. Additionally, the authors evaluated only suicidal attempts, a rarer phenomenon when compared to suicidal ideation. These limitations are possibly responsible for the discrepant results.

Conversely, suicidal behavior is similarly present in mixed states and depressive phases of BD. Only five papers comparing suicidal behavior between depressive and mixed phases were found and there was no significant statistical difference between groups in three of the five papers.^{30,32,33} The two remaining articles had contrasting results. Dilsaver et al.²⁷ found that suicidal behavior was more frequent among bipolar patients in depressive episodes when compared with patients in mixed states. In contrast, the study by Valtonen et al.³¹ showed that subjects in bipolar mixed states were more inclined to suicide than those in mixed depression, and

both groups had higher suicidality when compared to individuals in pure-depressive episodes.

Regarding the comparison of suicidal behavior in mixed states and in depressive episodes, we should note that only five of the selected studies performed such a comparison.^{27,30-33} Besides the small quantity of papers found, the number of patients involved in the analyses was also modest. For example, Valtonen et al.³¹ had only fifteen subjects in their mixed state sample, and Ciapparelli et al.³³ had only 23 patients in a major depressive episode. Moreover, it is statistically even harder to detect difference in suicidal behavior when comparing depressive episodes and mixed states since depression is a syndrome that incurs high risk of suicide. This difficulty is probably the reason for such a discrepancy among the results in our selection of studies.

A few papers have observed that the occurrence of manic symptoms could increase the risk of suicidal behavior in bipolar depression. Benazzi⁴⁰ verified that hypomanic symptoms such as thought acceleration, psychomotor agitation, and logorrhea were independent predictors of suicidal ideation in depressed individuals with BD type II. Additionally, Maj et al.⁴¹ showed that patients with BD type I presenting "agitated depression" according to RDC criteria had significantly more suicidal ideation than those with "non-agitated depression."

Although the link between impulsivity and BD is well established,⁴² its relation to suicidal behavior remains controversial and unclear. Swann et al.⁴³ observed that even modest manic symptoms during bipolar depressive episodes were associated with greater impulsivity, and with history of suicide attempts. In a 14-year follow-up study, Maser et al.⁴⁴ demonstrated that impulsivity is one of the best long-term predictors for suicide attempts and completion in bipolar patients. However, a literature review including 60 articles concluded that the association between suicidality and impulsivity in BD is less straightforward than often assumed.⁴⁵

Two systematic reviews showed higher levels of suicidal behavior in mixed states and depressive phases than in mania. The first review was performed by the International Society for Bipolar Disorder Task Force on Suicide in Bipolar Disorder.⁴⁶ They searched papers published since 1980, and one of their focuses was the incidence and characteristics of suicidal behavior. The systematic review revealed that both depressive and mixed states in BD were associated with higher probability of intra-episodic suicidal attempts. Suicidal attempts were between 18 and 62 times more frequent in depressive phases and between 27 and 74 times more frequent in mixed states when compared with pure mania. The second review, performed in Brazil, searched papers that dealt with assessing risk factors

for suicide in BD. They established that both depressive episodes and mixed episodes are strongly associated with suicidal behavior in this population.⁴⁷

The Jorvi Bipolar Study (JoBS) is a longitudinal prospective cohort study of patients diagnosed with BD type I and type II that investigated epidemiological aspects of BD. A paper based on the JoBS database analyzed data from 177 patients with BD who were prospectively followed for five years.⁴⁸ The authors made it clear that the incidence of suicidal attempts was higher during mixed and depressive phases of BD, when compared with mania and hypomania. Moreover, they showed that such incidence was higher during the mixed phases than during pure depression.

Notably none of the papers selected for this review evaluated deaths by suicide, which would perhaps be the most relevant analysis of suicidal behavior. Information on completed suicide is more frequently found in retrospective studies, since a prospective analysis of the matter is extremely unlikely. A retrospective study performed in Finland analyzed 52,747 hospitalizations and investigated deaths by suicide of patients with BD after discharge. Results showed that 0.3% of the hospitalizations caused by mania, 0.3% of the hospitalizations caused by a mixed episode, and 0.7% of those caused by a depressive episode resulted in suicide and occurred in up to 120 days after discharge.⁴⁹

The papers selected for this review defined mixed states in several different ways, and this could be an important limitation to be considered when interpreting the results. Nevertheless, the number of symptoms of the opposite pole experienced by individuals in a mixed episode had apparently little influence on their suicidal behavior. Therefore, we should be aware of the possibility that overly restrictive criteria in clinical practice may lead to under-diagnosis of mixed states as well as to neglect of the proper attitude towards prevention of suicide.

Furthermore, this review is subject to a few other limitations. Initially, publication bias, since modest results have a smaller probability of being published. Secondly, the lack of uniformity among studies because of sample heterogeneities, methodological variability, differences in assessing suicidal behavior, and differences in definitions of a mixed state. Thirdly, the absence of studies investigating completed suicide.

Despite these, the results hereby presented are worth considering in clinical practice in order to better evaluate suicide risk as well as to prevent suicide. Moreover, our findings show that there are few studies in the scientific literature that have properly investigated whether BD mixed states are associated with higher risk of suicidal behavior than pure depressive states.

Conclusion

In conclusion, results of clinical studies suggest that mixed states relate more intensely to suicidal behavior than episodes of pure mania in acute episodes of BD. However, it was not possible to demonstrate that mixed states are associated with higher risk of suicidal behavior than pure depressive states.

Disclosure

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