

Research paper

Prevalence of DSM-5 mixed features: A meta-analysis and systematic review

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ABSTRACT

Background: The definition of mixed features by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) remains controversial; however, there has been no systematic review of the prevalence of DSM-5 mixed features. We conducted a meta-analysis and systematic review to examine the prevalence of DSM-5-defined mixed features in major depressive episodes (MDE) and manic/hypomanic episodes.

Methods: We systematically searched all literature types (i.e., observational, cross-sectional, cohort, retrospective chart review, and post-hoc analysis) in electronic databases including MEDLINE, Embase, CINAHL, PsycINFO, and Web of Science from 2013 to 2020.

Results: A total of 17 studies with 20 samples were selected. The pooled prevalences of the mixed features in MDE and manic/hypomanic episodes were 11.6% (95% confidence interval [CI] = 7.9–16.7%) and 26.8 (95% CI = 17.0–39.5%), respectively. The prevalence of mixed features during major depressive disorder in East Asian countries was the lowest, which ranged from 0–2.2%. The subgroup analysis did not identify any influential factors for substantial heterogeneity. Most of the individual studies demonstrated moderate to high risk of bias.

Conclusions: Despite the increasing attention and controversy surrounding DSM-5-defined mixed features, few studies have systematically estimated the prevalence. Future studies with appropriate design and sample sizes should measure the prevalence of mixed features during MDE and manic/hypomanic episodes.

1. Introduction

In the history of the dichotomous classification of mood disorders (i.e., depression versus mania) in the Diagnostic and Statistical Manual of Mental Disorders (DSM), the term ‘mixed’ has long maintained its presence. In the DSM-III, the ‘mixed subtype’ initially referred to simultaneous or rapidly changing full criteria depressive symptoms through manic episodes of bipolar disorder (American Psychiatric Association, 1980). Although it was changed to ‘mixed episode’ in the DSM-IV, it was still conceptualized as depressive symptoms that occurred during manic episodes (American Psychiatric Association, 1994).

The DSM-5 led to two substantial changes to mixed states. First, it can now be used beyond bipolar disorder, particularly in major depressive disorder (MDD), which reflects the presence of manic episodes during major depressive episodes (MDE) (American Psychiatric Association, 2013). The second change is the threshold reduction for the opposite pole criteria. In the DSM-III, DSM-III-R, and DSM-IV, the full criteria of the MDE needed to be met during a manic episode to be

diagnosed with a mixed subtype; however, in the DSM-5, only three non-overlapping symptoms of the opposite pole are required.

These criteria for mixed features in the DSM-5 has caused global debates due to the exclusion of overlapping symptoms (Koukopoulos et al., 2013; Malhi et al., 2014; Park, 2018). The diagnostic criteria of mixed features during MDD require only three non-overlapping symptoms (i.e., elevated/expansive mood, grandiosity, talkativeness, a flight of idea, increased energy, increased activity, and decreased need for sleep). Other symptoms of a manic episode, such as psychomotor agitation and distractibility, do not need to be considered because they overlap with the criteria for MDE.

For decades, researchers have conceptualized mixed properties of depression in the DSM (Benazzi, 2008; Benazzi et al., 2004; Faedda et al., 2015). Mixed depression is characterized by psychomotor agitation, irritability, and distractibility and is considered to be the opposite side of melancholic depression, which is characterized by severe psychomotor retardation, anergia, and anhedonia (Malhi et al., 2014; Benazzi, 2006). Since the essential features of mixed depression have

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overlapping symptoms, both of which are present during MDE and manic episodes, the exclusion of overlapping symptoms from mixed features in the DSM-5 has been debated.

Researchers have questioned if DSM-5 mixed features can be diagnosed in clinical practice (Malhi et al., 2014; Park, 2018). Reports on their prevalence have widely varied from 0–46.5% (Takeshima and Oka, 2015; Hergueta and Weiller, 2013); however, no systematic approaches have investigated how the prevalence was measured and which factors influenced any discrepancies. Although a recent meta-analysis estimated the prevalence of mixed states in MDD and bipolar disorder (Vazquez et al., 2018), only four studies on DSM-5 mixed features were included.

Whereas the framework of the population, intervention, comparator and outcome, which is known as the PICO, is the most widely used format, according to the objective of this study (i.e., to estimate a prevalence of mixed features), we used the Condition, Context, Population (CoCoPop) format (Munn et al., 2015). The primary question was that: “In people with bipolar disorder and MDD, what is the prevalence of the mixed features according to the diagnosis and polarity?”

Based on the above study question, we conducted a systematic

review and meta-analysis to: (1) estimate the pooled prevalence of mixed features according to the DSM-5, (2) systematically explore qualitative properties of the individual studies, and (3) identify potential moderators for the discrepancies in the prevalence of mixed features.

2. Methods

The meta-analysis and systematic review was conducted according to both the Meta-Analysis of Observational Studies in Epidemiology guidelines (Stroup et al., 2000) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (Moher et al., 2010).

2.1. Eligibility criteria

We included all observational, cross-sectional, cohort, retrospective chart review, and *post-hoc* analysis studies that primarily aimed to measure the prevalence of mixed features as per the DSM-5 in MDE and manic/hypomanic episodes. The diagnostic criteria of the mixed features according to the DSM-5 is represented in the Supplementay

Table 1
Characteristics of the 20 samples included in the systematic review and meta-analysis.

Country	Author, year	Diagnosis	Study design	Recruitment methods	Diagnostic criteria	Diagnostic interview	Total sample	Age	Sex
Australia	Frankland, 2015	BD-I, BD-II, MDD	Retrospective chart review	Selective	DSM-IV	Diagnostic Interview for Genetic Studies version 2.0	366	49.6 (30.5–63.3 IQR)	69.2%
United States	Hasin, 2018	MDD	Original research	Probability sampling	DSM-5	AUDADIS-5	7432	29.05 ± 0.21 (18–)	NA
United Kingdom	Hergueta, 2013	BD-I	Original research	Selective	DSM-5	MINI	115	43.7 (18–)	53.9%
Canada	McIntyre, 2019	BD-I	Post-hoc analysis	Selective	DSM-IV-TR	YMRS, PANSS, MADRS	1037	39.9 (18–65)	56%
International	McIntyre, 2015	BD-I, BD-II, MDD	Post-hoc analysis	Selective	DSM-IV	MINI	982	NA	63.8%
International	McIntyre, 2013	BD-I	Post-hoc analysis	Selective	DSM-IV	YMRS, PANSS, MADRS	960	38.7	46.3%
International	Miller, 2016	BD-I, BD-II, BD-NOS, Schiaoaffective disorder-bipolar type	Post-hoc analysis	Selective	DSM-IV	SCID	907	41.2 ± 11.6	55.8%
United States	Perlis, 2014	MDD	Post-hoc analysis	Selective	DSM-IV	Clinical diagnosis with DSM-IV checklist	2397	40.7 ± 13.2 (18–75)	62.2%
International	Perugi, 2015	BD-I, BD-II	Original research	Consecutive	DSM-IV-TR		2811	44.5 ± 13.8	68.8%
Spain	Reinares, 2015	BD-I	Retrospective chart review	Selective	DSM-IV-TR	Clinical interview	169	42.5 ± 12.8 (18–)	46.2%
Korea	Shim, 2019	BD-I, BD-II, MDD	Retrospective chart review	All hospitalized patients	DSM-5	Clinical interview	859	47.3 ± 18.29 (19–)	61.8%
Korea	Shim, 2015	BD-I, BD-II, BD NOS	Retrospective chart review	All admitted patients	DSM-IV-TR	Clinical interview	371	26.37 ± 9.7 manic/hypomanic with mixed features 20.57 ± 2.9 depressed with mixed features (15–75)	63%
Japan	Shinzato, 2019	Depressive disorders and bipolar and related disorders	Original research	Consecutive	DSM-5	NA	154	(13–83)	56.2%
Japan	Takeshima, 2015	BD-II, BD-NOS, MDD	Original research	Consecutive	DSM-IV-TR	Clinical interviews	217	40 (16–88)	59%
United States	Tohen, 2017	BD-I, BD-II	Post-hoc analysis	Selective	DSM-IV-TR	MINI	482	38.9 ± 12.1 (19–67)	59.8%
International	Tohen, 2014	BD-I	Post-hoc analysis	Selective	DSM-IV-TR	MINI	514	36.0 (11.1) (18–64)	63%
		BD-I	Post-hoc analysis	Selective	DSM-IV	SCID	1072	41.8 (12.5) (18–)	52%
International	Young, 2015	BD-I	prospective	Consecutive	DSM-IV-TR	MINI	1035	40 (18–73)	

Abbreviations: BD-I: bipolar I disorder, BD-II: bipolar II disorder, MDD: major depressive disorder, DSM: Diagnostic and Statistical Manual, MINI: Mini International Neuropsychiatric Interview, YMRS: Young Mania Rating Scale, MADRS: Montgomery–Åsberg Depression Rating Scale, PANSS: Positive and Negative Syndrome Scale, BD NOS: bipolar disorder not otherwise specified, SCID: Structured Clinical Interview for DSM Disorders.

Note: Tohen, 2014 consists of two separate sets of clinical trials; therefore, we described them separately.

Table 1. We included studies that examined patients with MDD or BD at any age.

Studies were excluded if they met of the following criteria: (1) diagnosed primary mood disorder using only self-reported instruments, and (2) measured the prevalence among an already screened or referred group (e.g., only recruit individuals that are at risk for mixed features through self-report).

2.2. Information sources and search strategy

Literature was systematically searched from the following electronic databases: MEDLINE, Embase, CINAHL, and Scopus. The search was conducted by a mental health professional with knowledge and experience in systematic review and meta-analysis. The search period was set from 2013 to January 1, 2020. The search strategy for all databases was [mixed.mp. AND ((major depressive disorder.mp. or exp Depressive Disorder, Major/) OR (bipolar disorder.mp. or exp Bipolar Disorder/)) AND exp Diagnosis/]. There were no language restrictions imposed and languages other than English were translated using computer-assisted translation (i.e., Google Translate). We further selectively searched literature cited in the research to be reviewed along with systematic reviews and relevant news articles.

2.3. Selection process

Two authors, KSN and SEC, independently screened the titles and abstracts of the literature. KSN and SEC obtained full reports for all literature that appeared eligible based on inclusion criteria. Potentially eligible literature were also further assessed. When there were discrepancies between the two authors, a third author (JMK) resolved any disagreements. If the information contained within the literature was insufficient and/or there was uncertainty, one author (SEC) contacted the corresponding authors for clarification. If any duplicate data was suspected, the study with the larger sample size was selected.

2.4. Data items

Information on the age, sex, geographical region of study, number of participants, number if participants diagnosed with mixed features, methods used to diagnose mixed features, and the original study from which the samples with mixed features were extracted were collected.

2.5. Outcomes and prioritization

We extracted the total number of participants as well as the numbers of those diagnosed with mixed features. If only the percentage of study participants with mixed features was available, the number of participants with mixed features was calculated by multiplying the total sample size by the percentage given.

2.6. Assessment of the risk of bias

Each included study was assessed for methodological quality using the instruments for the meta-analysis of prevalence, which is comprised of 10 items plus a summary assessment (Hoy et al., 2012). The first four items assess the external validity, whereas the remaining six assess the internal validity, and the summary assessment evaluates the overall risk of bias.

2.7. Data synthesis

The prevalence of mixed features in each study was synthesized by using an odds ratio with a 95% confidential interval (CI). The random-effects model was used for estimating pooled prevalence. A test for heterogeneity was conducted using the Q statistic and I^2 . Generally, an I^2 of 0% indicates no observed heterogeneity, 25%, 50%, and 75%

represent low, moderate, and high heterogeneity, respectively (Higgins et al., 2003). Meta-regression and subgroup analyses were conducted to identify potential contributing factors to the prevalence. This was done by using pre-determined factors such as geographic region, type of diagnostic assessment tool used, type of diagnostic interviewing instrument used, recruitment methods, study design, and the primary diagnosis of MDE or manic/hypomanic episodes. Publication bias was visually inspected through funnel plot and Egger's methods (Egger et al., 1997). Subgroup analysis, meta-regression, and publication bias were assessed only if the number of included studies were 10 or more. All meta-analysis processes were conducted by Comprehensive Meta-Analysis (version 3; Biostat, Englewood, NJ, USA).

3. Results

3.1. Characteristics of the studies

A total of 17 studies and 20 samples were included. The flow chart is presented in the **Supplementary Figure 1**. **Table 1** shows the characteristics of the studies. The majority of studies were international ($n = 6$), followed by the United States ($n = 3$), Japan ($n = 2$), and Republic of Korea ($n = 2$).

The diagnosis of the primary mood disorder varied; bipolar disorder was found in 15 studies, whereas MDD was found in six studies. Only five studies conducted their research with a primary focus on the prevalence of mixed features, whereas the other 12 studies calculated the prevalence of mixed features retrospectively.

Other than one study (Hasin et al., 2018), the remaining studies did not consider the representation of the sampling sites. Notably, the sampling sites were selected conveniently. Only one study exploited probability sampling (Hasin et al., 2018), three studies recruited subjects consecutively, and two studies recruited all hospitalized patients within the study period; however, the remaining 11 studies recruited subjects selectively.

3.2. Risk of bias

Table 2 shows the risk of bias in the included studies. In the summary item of the overall risk of study bias, only two studies (11.76%) demonstrated a low risk of bias. A total of six studies (35.29%) were moderate, whereas nine (52.94%) had high risk. From the perspective of the individual items, only one study (Hasin et al., 2018) scored 'Yes' on Item 1, which evaluates whether the studies' target population was a close representation of the national population. Similarly, only the aforementioned study (Hasin et al., 2018) scored 'Yes' on Item 4, which means the response rate was more than 75%, or that no significant differences were seen between responders and non-responders.

Generally, post-hoc analyses of the psychopharmacological clinical trials had a high risk of bias (Hergueta and Weiller, 2013; McIntyre et al., 2015; McIntyre et al., 2019b; McIntyre et al., 2013; Miller et al., 2016; Perlis et al., 2014). In contrast, original research had a low (Hasin et al., 2018) to moderate risk of bias (Hergueta and Weiller, 2013; Perugi et al., 2015; Reinares et al., 2015; Shinzato et al., 2019; Takeshima and Oka, 2015).

3.3. Meta-analysis

Figs. 1 and 2 show forest plots of the prevalence of mixed features during MDE and manic/hypomanic episodes, respectively. In the MDE, the pooled prevalence of the mixed features was 11.6% (95% CI = 7.9%–16.7%). Two samples in the East Asian countries (Republic of Korea and Japan) had the lowest prevalence, which were 2.2% (12 out of 552) (Shim et al., 2019) and 0% (0 out of 125) (Takeshima and Oka, 2015), respectively.

In manic/hypomanic episodes, the pooled prevalence was 26.8% (95% CI = 17.0%–39.5%). One post-hoc analysis from the international

Table 2
Risk of bias of the included studies.

Study	1. Was the study's target population a close representation of the national population in relation to relevant variables?	2. Was the sampling frame a true or close representation of the target population?	3. Was some form of random selection used to select the sample, OR was a census undertaken?	4. Was the likelihood of nonresponse bias minimal?	5. Were data collected directly from the subjects (as opposed to a proxy)?	6. Was an acceptable case definition used in the study?	7. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	8. Was the same mode of data collection used for all subjects?	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	11. Summary item on the overall risk of study bias
Frankland	2015	No	Yes	Yes	No	No	Yes	No	Yes	No	Yes
Hasin	2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Hergueta	2013	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Low
McIntyre	2019	No	Yes	Yes	No	No	No	Yes	No	Yes	High
McIntyre	2015	No	No	No	No	No	No	Yes	No	Yes	High
McIntyre	2013	No	No	Yes	No	Yes	No	Yes	No	Yes	High
Miller	2016	No	Yes	No	No	Yes	No	Yes	Yes	Yes	High
Perlis	2014	No	Yes	No	No	No	No	Yes	No	Yes	High
Perugi	2015	No	Yes	Yes	No	Yes	Yes	No	No	Yes	Moderate
Reinares	2015	No	Yes	No	No	Yes	Yes	Yes	No	Yes	Moderate
Shim	2019	No	Yes	Yes	No	No	Yes	No	No	Yes	High
Shim	2015	No	Yes	Yes	No	No	Yes	No	No	No	High
Shinzato	2019	No	Yes	No	No	Yes	No	No	No	Yes	Moderate
Takeshima	2015	No	Yes	No	No	Yes	Yes	No	Yes	Yes	Moderate
Tohen	2017	No	Yes	Yes	No	No	Yes	Yes	Yes	No	Moderate
Tohen	2014	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Moderate
Young	2015	No	No	No	No	No	Yes	Yes	No	No	High

psychopharmacological study reported a prevalence of 81.3% (52 out of 64) (McIntyre et al., 2015). Unlike the prevalence in MDE, research conducted in the Republic of Korea showed a prevalence of 24.0% (52 out of 217).

When the meta-analysis is confined to the studies with low to moderate risk of bias, the pooled prevalence of mixed features decreased to 9.2% (95% CI = 5.4%–15.4%) in MDE and 21.6% (95% CI = 6.0%–54.1%) in manic/hypomanic episode, respectively (Supplementary Figure 2 and Supplementary Figure 3).

3.4. Subgroup and meta-regression analyses

As shown in Table 3, any subgroup analysis reduced heterogeneity. Subgroups in the region, diagnosis of primary mood disorder, design of the study, recruitment of the subjects, diagnostic criteria, and diagnostic interview for the primary mood disorder scored on I^2 above 75, which indicates significant heterogeneity.

Meta-regression analysis showed that potential moderators did not have a significant influence on the overall results in the meta-analysis (Table 4). The interaction effects of diagnosis by geographic region scored an R^2 of 0.69, which suggests that the interaction effects by diagnosis $\times$ geographic region explains 69% of the variance in the meta-analysis.

3.5. Publication bias

Supplementary Figure 4 shows funnel plots for the publication bias in the prevalence of mixed features during MDD. The results show that there does not appear to be small study effects; however, except for one study (Hasin et al., 2018) positioned in the left lower area of the funnel plot, all the remaining studies had a relatively small sample size.

Subgroup analysis, meta-regression, and funnel plots could not be conducted in mixed features during manic/hypomanic episodes due to the small number of samples ($n = 7$).

4. Discussion

We investigated the evidence for the prevalence of DSM-5-defined mixed features in MDE and manic/hypomanic episodes. The quantitative estimations of the prevalence of mixed features were 11.6% (95% CI = 7.9–16.7%) in MDE and 26.8% (95% CI = 17.0–39.5%) in manic/hypomanic episodes, respectively; however, there are several reasons that we should not merely accept the reported prevalence of mixed features. First, the heterogeneity issues were not solved by subgroup analysis; the heterogeneity was significant ($I^2 > 75$) in all subgroups. This suggests that there were influential factors for the prevalence of mixed features that were not included in the present meta-analysis. Second, the quality of the studies was generally low. In the assessment for the risk of bias, except for one study (Hasin et al., 2018), most of the remaining studies scored less than half of the total score. This low quality raises concern for if the calculated pooled prevalence is acceptable.

Alternatively, there are interesting findings regarding the prevalence of mixed features during MDD. Studies from East Asian countries (i.e., Republic of Korea and Japan) reported the prevalence of mixed features in MDD as extremely low, such as 2.2% (12/552) (Shim et al., 2019) and 0% (0/125) (Takeshima and Oka, 2015), respectively. This is sharply contrasted by the prevalence of two studies from the United States, which were 9.6% (231/2397) (Perlis et al., 2014) and 15.4% (69/448) (Hasin et al., 2018). We question what causes this discrepancy between Western and Eastern countries. Although we have insufficient studies to confirm this discrepancy, up-to-date evidence provides insight. It has been widely suggested that there is a difference in accepting and expressing emotion between Western and Eastern Asian cultures (De Vaus et al., 2018). Traditionally, suppression has been recommended in Eastern Asian cultures (Matsumoto et al., 2008). The suppression of

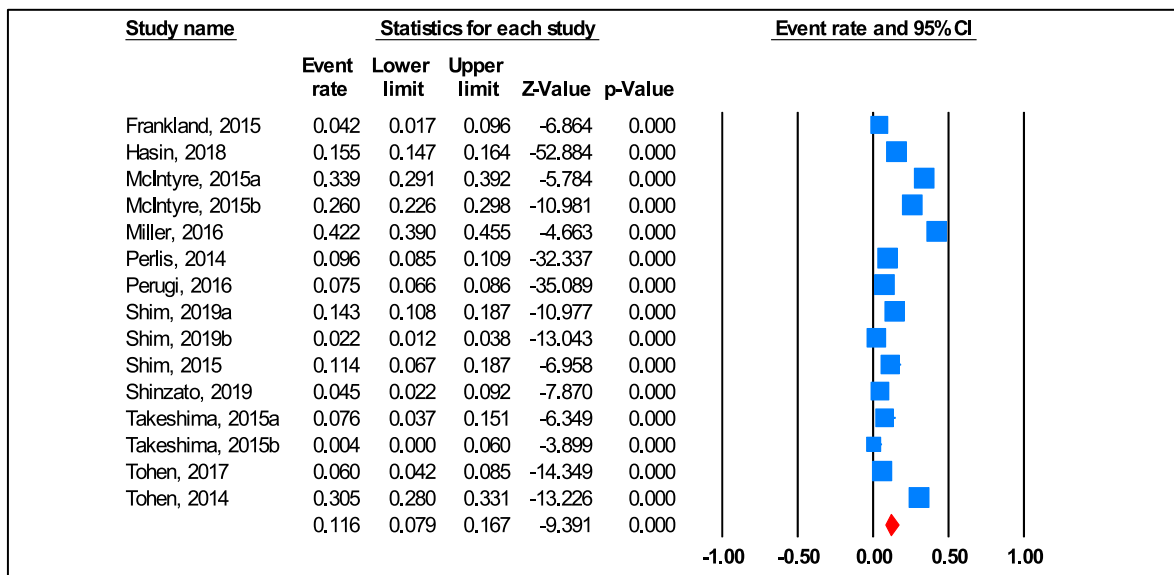


Fig. 1. Forest plot of the prevalence of mixed features in major depressive episode (MDE)

Notes: McIntyre 2015a, Shim 2019a, and Takeshima 2015a refer to MDE during bipolar disorder. McIntyre 2015b, Shim 2019b, and Takeshima 2015b refer to MDE during major depressive disorder.

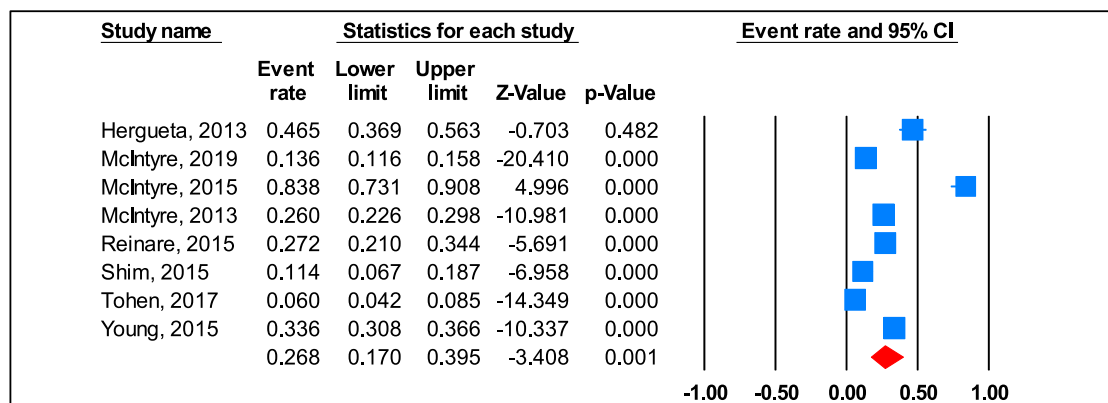


Fig. 2. Forest plot of the prevalence of mixed features in manic/hypomanic episodes.

negative emotion is a social norm in this society. Hence, it is unlikely that non-overlapping manic symptoms such as elevated/expansive mood, grandiosity, talkativeness, flight of idea, increased energy, increased activity, and decreased need for sleep would occur during MDE in MDD. Importantly, there has been uncertainty surrounding the clinical utility of DSM-5 mixed features in MDD, which exceeds three or more non-overlapping manic/hypomanic symptoms, but does not meet the full diagnostic criteria of manic/hypomanic episodes (Park, 2018). This cross-cultural discrepancy in the DSM-5 is not new. There is also uncertainty regarding whether the diagnostic criteria of MDD, which was developed and validated in Western culture, could reflect depressive symptoms in the East Asian culture (Chang et al., 2008). Further cross-cultural studies are required to address this.

However, the controversy surrounding the diagnostic validity of DSM-5-defined mixed features is not confined to the East Asian culture. As Pacchiarotti et al. (2020) recently argued, removing overlapping symptoms from the diagnostic criteria in the DSM-5 has resulted in the underdiagnosis of mixed features (Pacchiarotti et al., 2020). Another study conducted in Europe (Russia, Serbia, Ukraine, and United Kingdom) and the United States showed that overlapping symptoms were commonly reported in patients with mixed features during MDD (Targum et al., 2016). In said study, only flight of ideas (66.8%) and

pressured speech (61.1%) were more commonly reported than overlapping symptoms such as irritability (57.3%) and distractibility (59.2%) among patients with mixed features of MDD (Targum et al., 2016). Decreased need for sleep (40.8%), increased energy or goal-directed activity (28.0%), elevated/expansive mood (18.0%), excessive involvement in pleasurable activity (15.6%), and inflated self-esteem (6.6%) were all less reported than irritability and distractibility.

The present meta-analysis and systematic review could be regarded in terms of the clinical importance of mixed features in mood disorders. Traditionally, mixed features have had several clinical implications. First, mixed features are associated with severe clinical manifestations and poor prognosis. Studies have reported that DSM-5-defined mixed features have more severe symptoms, anxiety, suicidal ideation, suicidal plan, and impaired psychosocial function than other types of MDD (Hasin et al., 2018; Tohen et al., 2017). Second, therapeutic intervention for mixed features differs from those for typical MDE or manic/hypomanic episodes. Although the therapeutic intervention for mixed features in MDD has not been firmly established, most studies have recommended adding atypical antipsychotics or mood stabilizers to the antidepressant regimen (Verdolini et al., 2018). Importantly, the original post-hoc analyses we included investigated the efficacy and

Table 3

Subgroup analysis of the prevalence of mixed features during a major depressive episode.

Region		N	Prevalence	95% Lower	95% Upper	Q	p	I ²
Diagnosis	Australia	1	4.2%	1.7%	9.6%	0.0	1.000	0.0
	East Asia	6	5.7%	2.6%	12.1%	46.2	0.000	89.2
	International	5	25.5%	13.3%	43.4%	558.4	0.000	99.3
	United States	3	10.0%	6.3%	15.6%	75.4	0.000	97.3
Design	BD	7	18.2%	11.4%	27.8%	230.8	0.000	97.4
	BD+MDD	2	6.7%	4.3%	10.1%	1.9	0.171	46.6
	MDD	6	8.7%	5.4%	13.8%	173.5	0.000	97.1
Recruitment	Original research	5	7.5%	4.2%	13.1%	127.1	0.000	96.9
	Post-hoc analysis	6	21.5%	12.1%	35.2%	515.4	0.000	99.0
	Retrospective chart review	4	6.5%	2.5%	15.9%	40.6	0.000	92.6
Diagnostic criteria	All patients	3	7.3%	2.3%	20.8%	36.9	0.000	94.6
	Consecutive	4	6.1%	3.8%	9.8%	6.4	0.096	52.8
	Probability sampling	1	15.5%	14.7%	16.4%	0.0	1.000	0.0
	Selective	7	18.1%	10.3%	29.8%	535.1	0.000	98.9
Diagnostic interview	DSM-5	4	7.4%	3.6%	14.8%	63.6	0.000	95.3
	DSM-IV	3	13.5%	3.2%	43.0%	414.8	0.000	99.5
	DSM-IV-TR	8	13.0%	6.9%	23.0%	449.0	0.000	98.4
	Clinical interview	6	7.3%	4.4%	11.9%	42.7	0.000	88.3
	MINI	2	14.5%	2.5%	52.7%	91.2	0.000	98.9
	Others	5	11.2%	5.2%	22.5%	561.1	0.000	99.3
	YMRS, MADRS, PANSS	2	29.7%	22.6%	38.0%	6.4	0.011	84.5

Abbreviations: BD: bipolar disorder, MDD: major depressive disorder, DSM: Diagnostic and Statistical Manual, MINI: Mini International Neuropsychiatric Interview, YMRS: Young Mania Rating Scale, MADRS: Montgomery–Åsberg Depression Rating Scale, PANSS: Positive and Negative Syndrome Scale.

Table 4

Meta-regression analysis of the prevalence of mixed features during MDE.

	Coefficient	Standard Error	95% Lower	95% Upper	Z	p	R ²
Year	-0.1531	0.1767	-0.4994	0.1932	-0.87	0.3862	0
Region (reference = Australia)	East Asia	0.3697	0.9748	-1.5409	2.2802	0.38	0.7045
	International	2.0633	0.9692	0.1636	3.963	2.13	0.0333
	United States	0.9185	1.0117	-1.0645	2.9014	0.91	0.364
							0.2
Diagnosis (reference = BD)	BD+MDD	-1.1161	0.6354	-2.3614	0.1292	-1.76	0.0079
	MDD	-1.1029	0.5245	-2.1309	-0.0749	-2.1	0.0355
Sex	-3.8535	3.6067	-10.9225	3.2154	-1.07	0.2853	0
Recruitment (reference = probability sampling)	Post-hoc analysis	-1.2944	0.5146	0.2857	2.303	2.52	0.0119
	Retrospective chart review	-0.0674	0.5814	-1.2069	1.0722	-0.12	0.9078
Diagnostic criteria (reference = DSM-5)							0
	DSM-IV	0.723	0.8232	-0.8906	2.3365	0.88	0.3798
	DSM-IV-TR	0.618	0.6669	-0.6892	1.9251	0.93	0.3541
Diagnostic interview (reference = clinical interview)							0
	MINI	0.8667	0.7363	-0.5763	2.3097	1.18	0.2391
	YMRS, MADRS, PANSS	1.7763	0.7333	0.3391	3.2135	2.42	0.0154
	Others	0.5718	0.5647	-0.5351	1.6787	1.01	0.3113

Abbreviations: BD: bipolar disorder, MDD: major depressive disorder, DSM: Diagnostic and Statistical Manual, MINI: Mini International Neuropsychiatric Interview, YMRS: Young Mania Rating Scale, MADRS: Montgomery–Åsberg Depression Rating Scale, PANSS: Positive and Negative Syndrome Scale.

safety of the psychopharmacological interventions for patients with mixed features. McIntyre et al. reported the prevalence of mixed features by conducting a post-hoc analysis from clinical trial data with cariprazine (McIntyre et al., 2019a) and asenapine (McIntyre et al., 2013). Tohen and colleagues also conducted a post-hoc analysis from studies that investigated the efficacy and safety of various agents (Tohen et al., 2017) and olanzapine (Tohen et al., 2014).

The present meta-analysis and systematic review has several limitations. First, due to the shortage of original studies, the prevalence of mixed features during manic/hypomanic episodes was not analyzed by subgroup analysis and meta-regression. Second, only 35.3% (6/17) studies examined the prevalence of mixed features with a pre-determined study plan (Hasin et al., 2018; Hergueta and Weiller, 2013; Perugi et al., 2015; Shinzato et al., 2019; Takeshima and Oka,

2015; Young and Eberhard, 2015). The other 64.7% (11/17) studies estimated the prevalence of mixed features retrospectively by reviewing medical charts and records. Whether retrospective inspection could be a valid approach for estimating the prevalence of mixed features has remained controversial. For example, McIntyre et al. estimated the prevalence of mixed features based on the same retrospective approach in 2015 and 2019 (McIntyre et al., 2019a; McIntyre et al., 2015). While they concluded that estimating DSM-5-defined mixed features by using Youth Mania Rating Scale scores could be useful (McIntyre et al., 2015), they explicitly stated that their post-hoc analysis could not be an evaluation of DSM-5-defined mixed features criteria (McIntyre et al., 2019a). A large portion of the retrospective measurement of DSM-5-defined mixed features reflects that current research could not meet the demands of uncertainty. Third, most of the studies did not

consider the representativeness of their sample, except for one nationwide study that included probability sampling (Hasin et al., 2018). Most studies did not statistically consider the number and place of recruitment sites and recruited subjects selectively or consecutively. From an epidemiological perspective, such shortcomings are a fundamental issue for the estimated prevalence of mixed features. Fourth, while there is a lot of interest and controversy surrounding DSM-5 mixed features, most of the studies that report their prevalence are of moderate to high risk of bias, which does adequately demonstrate the validity. After excluding studies with high risk of bias, the prevalence of the mixed features decreased both in the MDE and manic/hypomanic groups. Whereas the discrepancies in the pooled prevalence seem to be modest (11.6% versus 9.2% in MDE and 26.8% versus 21.6% in manic/hypomanic episode), it is worth to investigate possible relationship between quality of study and the estimated prevalence. Additionally, rather than reviewing existing research data or medical records to retrospectively diagnose mixed features, it is necessary to design a plan in advance and systematically investigate the prevalence.

5. Conclusion

In summary, we revealed that the prevalence of mixed features was 11.6% (95% CI = 7.9–16.7%) in MDE and 26.8% in manic/hypomanic episodes (95% CI = 17.0–39.5%). Given the several fundamental shortcomings of the individual studies, such as retrospective measurement and selective recruitment of the subjects, the pooled prevalence should be considered tentatively. Future studies with a predetermined epidemiological approach should confirm the prevalence. Last, given the vast discrepancy in the prevalence of mixed features during MDD between East Asian and other regions, the essential nature of mixed features should be considered in terms of the cross-cultural perspective.

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CRediT authorship contribution statement

Kyoung-Sae Na: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Jae Myeong Kang:** Supervision, Validation, Writing - review & editing. **Seo-Eun Cho:** Data curation, Formal analysis, Investigation, Visualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors have indicated no financial conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jad.2020.12.149](https://doi.org/10.1016/j.jad.2020.12.149).

References

- American Psychiatric Association, 1980. *Diagnosis and Statistical Manual of Mental Disorders*, 3rd edition. American Psychiatric Association, Washington, DC.
- American Psychiatric Association, 1994. *Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Association, Washington, DC.
- American Psychiatric Association, 2013. *Diagnosis and Statistical Manual of Mental Disorders*, 5th edition. American Psychiatric Association, Washington, DC.
- Benazzi, F., 2006. Various forms of depression. *Dialogues Clin. Neurosci.* 8, 151–161.
- Benazzi, F., 2008. Defining mixed depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 32, 932–939.
- Benazzi, F., Koukopoulos, A., Akiskal, H.S., 2004. Toward a validation of a new definition of agitated depression as a bipolar mixed state (mixed depression). *Eur. Psychiatry* 19, 85–90.
- Chang, S.M., Hahm, B.J., Lee, J.Y., Shin, M.S., Jeon, H.J., Hong, J.P., Lee, H.B., Lee, D.W., Cho, M.J., 2008. Cross-national difference in the prevalence of depression caused by the diagnostic threshold. *J. Affect. Disord.* 106, 159–167.
- De Vauss, J., Hornsey, M.J., Kuppens, P., Bastian, B., 2018. Exploring the east-west divide in prevalence of affective disorder: a case for cultural differences in coping with negative emotion. *Pers. Soc. Psychol. Rev.* 22, 285–304.
- Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315, 629–634.
- Faedda, G.L., Marangoni, C., Reginaldi, D., 2015. Depressive mixed states: a reappraisal of Koukopoulos' criteria. *J. Affect. Disord.* 176, 18–23.
- Hasin, D.S., Sarvet, A.L., Meyers, J.L., Saha, T.D., Ruan, W.J., Stohl, M., Grant, B.F., 2018. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. *JAMA Psychiatry* 75, 336–346.
- Hergueta, T., Weiller, E., 2013. Evaluating depressive symptoms in hypomanic and manic episodes using a structured diagnostic tool: validation of a new mini international neuropsychiatric interview (M.I.N.I.) module for the DSM-5 'with mixed features' specifier. *Int. J. Bipolar Disord.* 1, 21.
- Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. *BMJ* 327, 557–560.
- Hoy, D., Brooks, P., Woolf, A., Blyth, F., March, L., Bain, C., Baker, P., Smith, E., Buchbinder, R., 2012. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J. Clin. Epidemiol.* 65, 934–939.
- Koukopoulos, A., Sani, G., Ghaemi, S.N., 2013. Mixed features of depression: why DSM-5 is wrong (and so was DSM-IV). *Br. J. Psychiatry* 203, 3–5.
- Malhi, G.S., Lampe, L., Coulston, C.M., Tanious, M., Bargh, D.M., Curran, G., Kuiper, S., Morgan, H., Fritz, K., 2014. Mixed state discrimination: a DSM problem that went go away? *J. Affect. Disord.* 158, 8–10.
- Matsumoto, D., Yoo, S.H., Nakagawa, S., 2008. Members of the multinational study of cultural display, R. Culture, emotion regulation, and adjustment. *J. Pers. Soc. Psychol.* 94, 925–937.
- McIntyre, R.S., Masand, P.S., Earley, W., Patel, M., 2019a. Cariprazine for the treatment of bipolar mania with mixed features: a post hoc pooled analysis of 3 trials. *J. Affect. Disord.* 257, 600–606.
- McIntyre, R.S., Soczynska, J.K., Cha, D.S., Woldeyohannes, H.O., Dale, R.S., Alsuwaidan, M.T., Gallagher, L.A., Mansur, R.B., Muzina, D.J., Carvalho, A., Kennedy, S.H., 2015. The prevalence and illness characteristics of DSM-5-defined "mixed feature specifier" in adults with major depressive disorder and bipolar disorder: results from the international mood disorders collaborative project. *J. Affect. Disord.* 172, 259–264.
- McIntyre, R.S., Suppes, T., Earley, W., Patel, M., Stahl, S.M., 2019b. Cariprazine efficacy in bipolar I depression with and without concurrent manic symptoms: post hoc analysis of 3 randomized, placebo-controlled studies. *CNS Spectr.* 1–9.
- McIntyre, R.S., Tohen, M., Berk, M., Zhao, J., Weiller, E., 2013. DSM-5 mixed specifier for manic episodes: evaluating the effect of depressive features on severity and treatment outcome using asenapine clinical trial data. *J. Affect. Disord.* 150, 378–383.
- Jr. Miller, S., Suppes, T., Mintz, J., Helleman, G., Frye, M.A., McElroy, S.L., Nolen, W.A., Kupka, R., Leverich, G.S., Grunze, H., Altschuler, L.L., Keck, P.E., Post, R.M., 2016. Mixed depression in bipolar disorder: prevalence rate and clinical correlates during naturalistic follow-up in the stanley bipolar network. *Am. J. Psychiatry* 173, 1015–1023.
- Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, P., 2010. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int. J. Surg.* 8, 336–341.
- Munn, Z., Moola, S., Lisy, K., Riitano, D., Tufanaru, C., 2015. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *Int. J. Evid. Based Healthc.* 13, 147–153.
- Pacchiarotti, I., Kotzalidis, G.D., Murru, A., Mazzarini, L., Rapinesi, C., Valenti, M., Annella, G., Gomes-da-Costa, S., Gimenez, A., Llach, C., Perugi, G., Vieta, E., Verdolini, N., 2020. Mixed features in depression: the unmet needs of diagnosis and statistical manual of mental disorders fifth edition. *Psychiatry Clin. North Am.* 43, 59–68.
- Park, Y.M., 2018. The mixed-features specifier of major depressive disorder in DSM-5: is it practical? *Psychiatry Investig.* 15, 1009–1010.
- Perlis, R.H., Cusin, C., Fava, M., 2014. Proposed DSM-5 mixed features are associated with greater likelihood of remission in out-patients with major depressive disorder. *Psychol. Med.* 44, 1361–1367.
- Perugi, G., Angst, J., Azorin, J.M., Bowden, C.L., Mosolov, S., Reis, J., Vieta, E., Young, A.H., Group, B.R.-I.-M.S., 2015. Mixed features in patients with a major depressive episode: the BRIDGE-II-MIX study. *J. Clin. Psychiatry* 76, e351–e358.
- Reinares, M., Bonnin Cdel, M., Hidalgo-Mazzei, D., Undurraga, J., Mur, M., Nieto, E., Saez, C., Vieta, E., 2015. Making sense of DSM-5 mania with depressive features. *Aust. N. Z. J. Psychiatry* 49, 540–549.
- Shim, I.H., Lee, J., Kim, M.D., Jung, Y.E., Min, K.J., Kwon, Y.J., Kim, J.S., Lee, K., Woo, Y.S., Nam, B., Seo, J.S., Lee, J.G., Jon, D.I., Sohn, I., Park, S.Y., Yoon, B.H., Bahk, W.M., 2019. The prevalence and diagnostic classification of mixed features in patients with major depressive episodes: a multicenter study based on the DSM-5. *Int. J. Methods Psychiatry Res.* 28, e1773.
- Shinzato, H., Koda, M., Nakamura, A., Kondo, T., 2019. Development of the 12-item questionnaire for quantitative assessment of depressive mixed state (DMX-12). *Neuropsychiatr. Dis. Treat* 15, 1983–1991.
- Stroup, D.F., Berlin, J.A., Morton, S.C., Olkin, I., Williamson, G.D., Rennie, D., Moher, D., Becker, B.J., Sipe, T.A., Thacker, S.B., 2000. Meta-analysis of observational studies in

- epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA* 283, 2008–2012.
- Takeshima, M., Oka, T., 2015. DSM-5-defined 'mixed features' and Benazzi's mixed depression: which is practically useful to discriminate bipolar disorder from unipolar depression in patients with depression? *Psychiatry Clin. Neurosci.* 69, 109–116.
- Targum, S.D., Suppes, T., Pendergrass, J.C., Lee, S., Silva, R., Cucchiari, J., Loebel, A., 2016. Major depressive disorder with subthreshold hypomania (mixed features): clinical characteristics of patients entered in a multiregional, placebo-controlled study. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 68, 9–14.
- Tohen, M., Gold, A.K., Sylvia, L.G., Montana, R.E., McElroy, S.L., Thase, M.E., Rabideau, D.J., Nierenberg, A.A., Reilly-Harrington, N.A., Friedman, E.S., Shelton, R.C., Bowden, C.L., Singh, V., Deckersbach, T., Ketter, T.A., Calabrese, J.R., Bobo, W.V., McInnis, M.G., 2017. Bipolar mixed features - results from the comparative effectiveness for bipolar disorder (bipolar CHOICE) study. *J. Affect. Disord.* 217, 183–189.
- Tohen, M., Kanba, S., McIntyre, R.S., Fujikoshi, S., Katagiri, H., 2014. Efficacy of olanzapine monotherapy in the treatment of bipolar depression with mixed features. *J. Affect. Disord.* 164, 57–62.
- Vazquez, G.H., Lolich, M., Cabrera, C., Jokic, R., Kolar, D., Tondo, L., Baldessarini, R.J., 2018. Mixed symptoms in major depressive and bipolar disorders: a systematic review. *J. Affect. Disord.* 225, 756–760.
- Verdolini, N., Hidalgo-Mazzei, D., Murru, A., Pacchiarotti, I., Samalin, L., Young, A.H., Vieta, E., Carvalho, A.F., 2018. Mixed states in bipolar and major depressive disorders: systematic review and quality appraisal of guidelines. *Acta Psychiatrica Scand.* 138, 196–222.
- Young, A.H., Eberhard, J., 2015. Evaluating depressive symptoms in mania: a naturalistic study of patients with bipolar disorder. *Neuropsychiatr. Dis. Treat.* 11, 1137–1143.