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The clinical utility and relevance in clinical practice of DSM-5 specifiers for major depressive disorder: A Delphi expert consensus study

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ABSTRACT

Major depressive disorder (MDD) is a heterogeneous syndrome, associated with different levels of severity and impairment on the personal functioning for each patient. Classification systems in psychiatry, including ICD-11 and DSM-5, are used by clinicians in order to simplify the complexity of clinical manifestations. In particular, the DSM-5 introduced specifiers, subtypes, severity ratings, and cross-cutting symptom assessments allowing clinicians to better describe the specific clinical features of each patient. However, the use of DSM-5 specifiers for major depressive disorder in ordinary clinical practice is quite heterogeneous.

The present study, using a Delphi method, aims to evaluate the consensus of a representative group of expert psychiatrists on a series of statements regarding the clinical utility and relevance of DSM-5 specifiers for major depressive disorder in ordinary clinical practice. Experts reached an almost perfect agreement on statements related to the use and clinical utility of DSM-5 specifiers in ordinary clinical practice. In particular, a complete consensus was found regarding the clinical utility for ordinary clinical practice of using DSM-5 specifiers. The use of specifiers is considered a first step toward a "dimensional" approach to the diagnosis of mental disorders.

1. Introduction

According to the most recent statistics [1], more than 264 million people worldwide are affected from major depressive disorder (MDD). By the year 2030, MDD is expected to be the leading cause of disease burden around the world, accounting for 2.5% of global disability-adjusted life years lost (DALYs). About 30 million of people suffer from MDD in Europe, and one out of five US adults report lifetime symptoms of depression [2–4]. MDD is associated with a very high mortality risk, mainly due to suicide [5,6] and physical disorders, such as cardiovascular diseases (CVD) [7–9].

As heterogeneous syndrome, major depression is associated with different levels of severity and impairment on the personal functioning for each patient. Therefore, an appropriate clinical characterization of each individual patient should be made on the basis of several variables. These can be grouped into three main categories: a) patient-related variables, such as age, personal history, family history, antecedent environmental factors, recent environmental factors, personality traits and coping strategies, cognitive schemas and levels of social functioning [10–13]; b) illness-related factors, including symptoms, neurocognition, illness severity, clinical staging, physical comorbidities, duration of illness and duration of untreated illness, number of episodes [14,15]; and c) contextual-related factors, including access to care, social network and therapeutic relationship [16–21]. The evaluation of such variables is essential to develop individualized treatment plans aiming to treat the "person" with depression and not the "depressive illness" [22,23].

The two main classification systems used in psychiatry are the

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Diagnostic and Statistical Manual of Mental Disorders (DSM), published by the American Psychiatric Association (APA) and the International Classification of Diseases (ICD), published by the World Health Organization (WHO) [24,25]. The latest version of the DSM has been released in 2013 by the APA (with a subsequent revision in 2022) [26], while the eleventh revision of the ICD by the WHO has been completed in 2018, approved by the WHO General Assembly in 2019 and it is now being translated into several languages [27–29]. Although the last two editions of both manuals pointed to the harmonization between the two systems, some differences persist. While the DSM has the global aim to be used in scientific research settings, the ICD aims to improve the clinical utility of the different diagnoses in the clinical practice [30–33]. The DSM-5 introduced the differentiation between "subtypes" and "specifiers" [34], defining "subtypes" as "mutually exclusive and jointly exhaustive phenomenological subgroups within a diagnosis", while "specifiers" are defined by the lack of such features, while capturing parameters such as course, severity and/or descriptive features [35]. Specifiers and subtypes delineate phenomenological variants of a given disorder, which impact - among other outcomes - on treatment plans and treatment developments. Although the number of specifiers and subtypes included in the DSM-5 has been expanded in order to provide a more "dimensional" approach to mental disorders, the diagnostic approach proposed by the DSM-5 is still the "categorical" one, with the diagnosis being dependent on a "yes or no" decision [36–38]. However, the introduction of specifiers, subtypes, severity ratings, and cross-cutting symptom assessments allows clinicians to better describe the specific clinical features of each individual patient, representing a first decisive step for the development of personalized treatment plans.

Within the chapter of depressive disorders, the specifiers included are "with mixed features", "with anxiety symptoms", "with melancholic features" and "with atypical features", with the latter being the oldest and most widely studied [39].

These specifiers for MDD have been widely studied in clinical trials. Hasin et al. [40] in a national representative sample of US adult population found that the "with anxious/distress specifier " characterizes 74.6% of MDD patients, and the "with mixed features" specifier characterizes 15.5% of the same sample. Both specifiers are associated with early onset, worse outcome in terms of poor functioning, and suicidality, after controlling for the severity of illness.

The use of the other specifiers (i.e., those related to melancholic and atypical features) seems to be more controversial, as pointed out by Lorenzo-Luaces et al. [41], who concluded that the use of the DSM specifiers for atypical and melancholic features does not identify for a more homogeneous group of patients.

Based on such premises, the present study aims to evaluate the consensus of a representative group of expert psychiatrists on a series of statements regarding the clinical utility and relevance of DSM-5 specifiers for MDD in ordinary clinical practice.

2. Materials and methods

The Delphi method is a structured technique aimed to obtain a consensus opinion from a panel of experts by repeated rounds of questionnaires in areas where the evidence is scarce, and opinion is important [42].

A Steering Committee, composed by key opinion leaders (KOLs) in the fields of diagnosis and treatment of depression and other severe mental disorders based in Italy, identified the following main subtopics dealing with the DSM-5 specifiers for depressive disorders: use of DSM-5 specifiers in ordinary clinical practice, their clinical utility, their role in supporting the process of differential diagnosis, and in selecting the most appropriate pharmacological treatment.

The development of the Delphi survey followed a multi-step procedure: 1) analysis of the available literature and discussion on the use of DSM-5 specifiers for MDD in the clinical practice by KOL; 2) identification of an initial list of relevant topics, which was circulated among the members of the Steering Committee in order to obtain their feedbacks; 3) submission of the final draft of the Delphi questionnaire to external validators (see Acknowledgment for panel members' names) for revision/approval; 4) distribution of the final version of the Delphi questionnaire to participants of the expert panel.

The Delphi Questionnaire consists of 73 items (Table 1) grouped in sub-areas, according to the different specifiers listed in the DSM-5. In particular, the following specifiers "with anxiety feature", "with mixed features", "with melancholic features", "with atypical features", "with psychotic features", "with catatonia" have been considered. Moreover, four additional statements on the use and utility of DSM-5 specifiers in clinical practice have been added.

For each statement of the questionnaire, the participant had to express his/her level of agreement according to the following 5-point Likert scale: 1 = strongly disagree; 2 = disagree; 3 = agree; 4 = more than agree; 5 = strongly agree. In accordance with the Delphi standards, a consensus is reached when the sum of items 1 and 2 (Disagreement) or that of 3, 4, and 5 (Agreement) reaches the threshold of 66%. When the sum of the responses for a negative (1 and 2) or a positive consensus (3, 4, and 5) is below 66%, the consensus is not reached [43].

In the present study, the consensus process consisted of a two-step web-based Delphi method, which took place between February and May 2023.

The panel of experts were invited to fill in the questionnaire in February 2023. They received a brief introduction to the project with its objectives and process, and a link to fill in the questionnaire. Participants had about one hour to complete the questionnaire. For the statements and items on which consensus had not been achieved, panelists were asked to rate them again in a second round in May 2023.

Personal data collected included gender and years of experience in psychiatry. All data were anonymously analyzed.

3. Results

The questionnaire was delivered to an expert panel of 38 Italian psychiatrists using a modified Delphi method. Participants were experts in the treatment of depressive disorders, selected on the basis of their clinical experience and expertise.

Sixty percent of experts ($N = 23$) are male, with a mean experience in the field of psychiatry ranging from 16 to 25 years, mainly working in university hospital settings ($N = 20$).

At the first round of the Delphi survey, agreement was not reached for 20 items (out of 73). At the second round, panelists' agreement on statements was very high, with a consensus reached for almost all statements (the threshold was not reached for five items only). A positive agreement was reached for 43 items (58.9% of cases), while a negative agreement was obtained for 23 items (31.5% of cases) (Fig. 1).

A strong agreement (higher than 85%) was reached for 24 items, suggesting a shared view on the use and utility of DSM-5 specifiers for depressive disorders. An agreement higher than 70% was reached for 38 items (52.7%). All the statements and items of the consensus, indicating the percentages of agreement and disagreement, are reported in Table 1.

As regards the statements dealing with the use of specifiers (regardless the specific subtype), an almost perfect agreement (ranging from 100% to 71%) was reached, with the vast majority of participants reporting that the specifiers are adopted and are useful in ordinary clinical practice, supporting the clinical characterization of the individual patient and the differential diagnosis among the various affective disorders.

Statements related to the specifier "with anxiety features" reached a good level of positive agreement, in terms of relevance (for the choice of pharmacological treatment including an antidepressant drug with anxiolytic properties; 97%), utility (for reducing the rate of simultaneous diagnosis of anxiety and depressive disorders; 87%) and in terms of frequency of use in clinical practice (74%). A negative agreement was reached only for one statement ("utility in supporting appropriate

Table 1
Delphi Survey - DSM-5 Specifiers for Major Depressive Episode.

1 – General aspects
Specifiers introduced by DSM-5 – With anxious distress; With mixed features; With melancholic features; With atypical features; With psychotic features; With catatonia – for Major Depressive Episode

	Level of agreement					
	Disagreement		Agreement			
	1	2	3	4	5	Total
…are useful in daily clinical practice	5%			95%		100%
	0	2	22	8	6	38
… some of them are routinely used in clinical practice	0%			100%		100%
	0	0	9	19	10	38
… enable an appropriate clinical characterization of the individual case of MDD patient	29%			71%		100%
	1	10	14	10	3	38
…some of them are useful in the process of differential diagnosis between major depression and other mental disorders	13%			87%		100%
	0	5	7	17	9	38

2 – Specifier "with anxious distress"

	Level of agreement					
	Disagreement		Agreement			
	1	2	3	4	5	Total
… is used in clinical practice	26%			74%		100%
	3	7	17	9	2	38
… enables the clinical characterization of the individual patient	82%			18%		100%
	11	20	2	3	2	38
… its use could result in a reduced comorbidity rate between anxiety and depressive disorders	13%			87%		100%
	0	5	7	20	6	38
… allows the differential diagnosis between depressive and anxiety disorders	26%			74%		100%
	1	9	12	14	2	38
When using the specifier "with anxious distress", patient's pharmacological treatment usually includes an anxiolytic drug (e.g., benzodiazepine) as add-on	21%			79%		100%
	2	6	16	12	2	38
When using the specifier "with anxious distress", patient's pharmacological treatment usually includes an antidepressant drug with strong anxiolytic properties	3%			97%		100%
	1	0	13	18	6	38
When using the specifier "with anxious distress", patient's pharmacological treatment usually includes a mood stabilizer and/or an atypical antipsychotic drug	61%			39%		100%
	7	16	6	6	3	38

3 – Specifier "with mixed features"

	Level of agreement					
	Disagreement		Agreement			
	1	2	3	4	5	Total
… is used in clinical practice	21%			79%		100%
	3	5	15	11	4	38
… enables the clinical characterization of the individual patient	24%			76%		100%
	1	8	17	11	1	38
… it is useful for the differential diagnosis between depressive and bipolar disorders	18%			82%		100%
	2	5	7	15	9	38
When using the specifier "with mixed features", patient's pharmacological treatment usually includes an antidepressant drug	61%			39%		100%
	10	13	8	6	1	38
When using the specifier "with mixed features", patient's pharmacological treatment usually includes a mood stabilizer drug	5%			95%		100%
	1	1	12	14	10	38
When using the specifier "with mixed features", patient's pharmacological treatment usually includes lithium as mood stabilizer drug	21%			79%		100%
	2	6	9	15	6	38

4 – Specifier "with melancholic features"

	Level of agreement					
	Disagreement		Agreement			
	1	2	3	4	5	Total
… will lead a reduction of the comorbidity rate between depressive and bipolar disorders	82%			18%		100%
	9	22	4	2	1	38
… enables the identification of patients suffering from "difficult to treat" depression	32%			68%		100%
	0	12	12	13	1	38
… will enable an appropriate description of depression with severe anhedonic component	8%			92%		100%
	0	3	20	10	5	38
… could be helpful to identify patients at high suicidal risk	5%			95%		100%
	0	2	13	12	11	38
… could be helpful to identify patients at high hospitalization risk	18%			82%		100%
	0	7	8	11	12	38
… is used in clinical practice	18%			82%		100%

(*continued on next page*)

Table 1 (*continued*)

4 – Specifier "with melancholic features"

	Level of agreement					
	Disagreement		Agreement			
	1	2	3	4	5	Total
… enables the clinical characterization of the individual patient	1	6	12	15	4	38
		24%		76%		100%
… it is useful for the differential diagnosis between depressive and bipolar disorders	0	9	21	5	3	38
		68%		32%		100%
… it is useful to discriminate patients suffering from depression vs those suffering from bipolar disorder	3	23	11	1	0	38
		82%		18%		100%
… it is appropriate for the differential diagnosis between depressive and bipolar disorders	4	27	5	1	1	38
		76%		24%		100%
When using the specifier "with melancholic features", patient's pharmacological treatment usually includes a specific antidepressant class	5	24	9	0	0	38
		21%		79%		100%
When using the specifier "with melancholic features", patient's pharmacological treatment usually includes a mood stabilizer drug as add-on	0	8	13	15	2	38
		74%		26%		100%
When using the specifier "with melancholic features", patient's pharmacological treatment usually includes lithium as add-on mood stabilizer drug	1	27	6	4	0	38
		66%		34%		100%
When using the specifier "with melancholic features", avoid using drug with monoaminergic mechanism of action	1	24	8	4	1	38
		76%		24%		100%
When using the specifier "with melancholic features", pharmacological treatments are used at high dose (especially antidepressants)	4	25	5	3	1	38
		18%		82%		100%
… will lead a reduction of the comorbidity rate between depressive and bipolar disorders	0	7	18	11	2	38
		84%		16%		100%
… enables the identification of patients suffering from "difficult to treat" depression	4	28	5	1	0	38
		18%		82%		100%
	1	6	15	11	5	38

5 – Specifier "with atypical features"

	Level of agreement					
	Disagreement		Agreement			
	1	2	3	4	5	Total
… is used in clinical practice		24%		76%		100%
…enables the clinical characterization of the individual patient	2	7	11	15	3	38
		24%		76%		100%
… it is useful for the differential diagnosis between depressive and bipolar disorders	2	7	11	15	3	38
		68%		32%		100%
… it is useful to discriminate patients suffering from depression vs those suffering from bipolar disorder	3	23	10	1	1	38
		71%		29%		100%
… it should be appropriate to discriminate between patients suffering from depressive disorders and those with comorbid anxiety disorders	4	23	9	1	1	38
		55%		45%		100%
When using the specifier "with atypical features", patient's pharmacological treatment usually includes a specific antidepressant class	2	19	10	6	1	38
		47%		53%		100%
When using the specifier "with atypical features", patient's pharmacological treatment usually includes a mood stabilizer drug as add-on	3	15	9	7	4	38
		50%		50%		100%
When using the specifier "with atypical features", patient's pharmacological treatment usually includes lithium as add-on mood stabilizer drug	3	16	9	8	2	38
		53%		47%		100%
When using the specifier "with atypical features", patient's pharmacological treatment usually includes benzodiazepines as add-on treatment	2	18	11	7	0	38
		84%		16%		100%
When using the specifier "with atypical features", avoid using drug with monoaminergic mechanism of action	4	28	5	1	0	38
		74%		26%		100%
When using the specifier "with atypical features", patient's pharmacological treatment usually includes antipsychotic medication as add-on treatment	2	26	9	0	1	38
		42%		58%		100%
When using the specifier "with atypical features", pharmacological treatments are used at high dose (especially antidepressants)	2	14	12	10	0	38
		76%		24%		100%
… will lead a reduction of the comorbidity rate between depressive and above mentioned disorders	3	26	4	3	2	38
		68%		32%		100%
… enables the identification of patients suffering from "difficult to treat" depression	1	25	8	3	1	38
		32%		68%		100%
	1	11	18	6	2	38

6 – Specifier "with psychotic features"

	Level of agreement	
	Disagreement	Agreement

(*continued on next page*)

Table 1 (*continued*)

6 – Specifier "with psychotic features"

	Level of agreement					
	Disagreement		Agreement			
	1	2	3	4	5	Totale
	1	**2**	**3**	**4**	**5**	**Totale**
… is used in clinical practice		5%		95%		100%
	1	1	11	16	9	38
… enables the clinical characterization of the individual patient		8%		92%		100%
	1	2	16	15	4	38
… it is useful for the differential diagnosis process		5%		95%		100%
	0	2	4	23	9	38
… it is used, by reporting whether psychotic symptoms are congruent with mood (or not congruent)		18%		82%		100%
	2	5	14	12	5	38
When using the specifier "with psychotic features", patient's pharmacological treatment usually includes an antidepressant drug with a good safety (esp. cardiovascular) and tolerability profile		3%		97%		100%
	1	0	14	14	9	38
When using the specifier "with psychotic features", patient's pharmacological treatment usually includes a mood stabilizer drug as add-on		71%		29%		100%
	2	25	9	0	2	38
When using the specifier "with psychotic features", patient's pharmacological treatment usually includes antipsychotic drug as add-on treatment		0%		100%		100%
	0	0	13	12	13	38
… will lead a reduction of the comorbidity rate between affective and schizoaffective disorders		8%		92%		100%
	0	3	6	23	6	38
… enables the identification of patients suffering from "difficult to treat" depression		18%		82%		100%
	1	6	18	11	2	38

7 – Specifier "with catatonia"

	Level of agreement					
	Disagreement		Agreement			
	1	2	3	4	5	Total
… is used in clinical practice		32%		68%		100%
	1	11	16	6	4	38
… enables the clinical characterization of the individual patient		21%		79%		100%
	1	7	15	11	4	38
… it is useful for the differential diagnosis process among depressive disorder, bipolar disorder and schizoaffective disorder		76%		24%		100%
	3	26	8	1	0	38
… it is sufficient to capture the heterogeneity of psychomotor manifestation		87%		13%		100%
	10	23	1	2	2	38
When using the specifier "with catatonia", patient's pharmacological treatment usually includes an antidepressant drug with a good safety (esp. cardiovascular) and tolerability profile		26%		74%		100%
	2	8	22	5	1	38
When using the specifier "with catatonia", patient's pharmacological treatment usually includes a mood stabilizer drug as add-on		79%		21%		100%
	0	30	7	1	0	38
When using the specifier "with catatonia", patient's pharmacological treatment usually includes lithium as add-on mood stabilizer drug		79%		21%		100%
	1	29	7	1	0	38
When using the specifier "with catatonia", patient's pharmacological treatment usually includes benzodiazepines as add-on treatment		16%		84%		100%
	1	5	16	8	8	38
When using the specifier "with catatonia", avoid using drug with monoaminergic mechanism of action		68%		32%		100%
	0	26	10	2	0	38
When using the specifier "with catatonia", patient's pharmacological treatment usually includes antipsychotic drug as add-on treatment		32%		68%		100%
	0	12	21	4	1	38
When using the specifier "with catatonia", pharmacological treatments are used at high dose (especially antidepressants)		32%		68%		100%
	0	12	18	7	1	38
When using the specifier "with catatonia", patient's pharmacological treatment usually includes antidepressants + benzodiazepines		24%		76%		100%
	1	8	14	11	4	38
When using the specifier "with catatonia", patient's pharmacological treatment usually includes antidepressants + antipsychotics		32%		68%		100%
	0	12	19	6	1	38
When using the specifier "with catatonia", patient's pharmacological treatment usually includes antidepressants + mood stabilizers		68%		32%		100%
	1	25	11	1	0	38
… will lead a reduction of the comorbidity rate between affective and schizoaffective disorders	74%		26%			100%
	3	25	9	1	0	38
… enables the identification of patients suffering from "difficult to treat" depression		18%		82%		100%
	1	6	15	8	8	38

description of the individual clinical case") (82%).

As regards statements on the "with mixed features" specifier, consensus was not reached only for one statement. A high consensus was reached for statements dealing with the utility of "mixed features specifier" for selecting a pharmacological treatment with mood stabilizer (95%) and for the differential diagnosis between unipolar and bipolar depression (82%).

Statements related to the specifier "with melancholic features" reached a satisfying level of agreement. In particular, a negative agreement was found for items related to the utility of melancholic

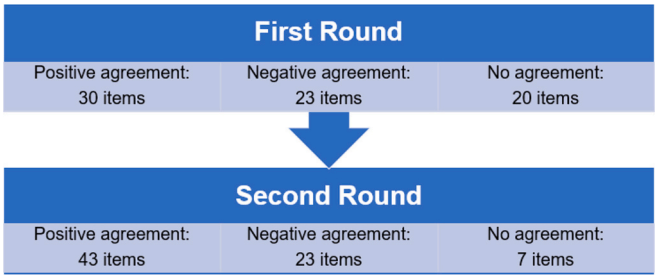

Fig. 1. Delphi process.

specifier for the differential diagnosis between unipolar and bipolar depression and for supporting the choice of the appropriate pharmacological treatment. A strong positive consensus (82–95%) was shared by experts in terms of relevance for identifying people suffering from depression with marked anhedonic features, or with significant suicidal risk or with "difficult to treat" depression.

The highest rate of no consensus was reached ($N = 5$ statements) for the statements dealing with the "with atypical features" specifier compared to statements related to the other specifiers. A good level of no consensus was obtained for statements related to the utility of this specifier in orienting the choice of pharmacological treatment (84%) and to the differential diagnosis of unipolar vs. bipolar depression (68%).

Statements dealing with the specifier "with psychotic features" reached an almost complete agreement, with values ranging from 82% (used for describing "difficult to treat patients") to 100% of agreement (pharmacological treatment including an antipsychotic drug).

As regards statements related to the specifier "with catatonic features", a positive agreement ranging from 68% (for statements related to its use in clinical practice and its utility in the selection of pharmacological treatments) to 84% (utility for discriminating people with difficult to treat depression) was reached. A negative consensus was found (74%) only for the item dealing with reduction of comorbidity rates between depression and schizoaffective disorder.

4. Discussion

This paper aims to evaluate the level of consensus in a representative group of experts about a series of statements on DSM-5 specifiers for depressive disorders and their utility and validity in clinical practice. Although the use of specifiers is highly controversial and debated from a clinical and research viewpoint, involved experts reached a significant level of consensus on the majority of statements.

Experts reached an almost perfect agreement on statements related to the use and clinical utility of DSM-5 specifiers in ordinary clinical practice. In particular, a complete consensus was found regarding the clinical utility for ordinary clinical practice of using DSM-5 specifiers. This finding is in line with those coming from other studies [40,44–46], confirming that the specifiers are useful for the clinical characterization of the individual patients and for formulating appropriate diagnoses. Furthermore, the use of specifiers is considered a first step toward a "dimensional" approach to the diagnosis of mental disorders, as outlined already by several authors [47–49].

A good level of positive agreement was found for the specifier "with anxiety features", in particular as regards its usefulness for the choice of a pharmacological treatment based on an antidepressant drug with anxiolytic properties. This finding is in line with that by Otsubo et al. [46], who showed that the evaluation of the DSM-5 anxiety specifier is relevant not only for the pharmacological and non-pharmacological management in the acute phase of the disorder but also in the continuation/maintenance treatment phase of patients with MDD. In line with the ongoing debate on the representativeness of the anxious specifier [50], a negative consensus was reached on the statement about its clinical utility. Although the validity of the anxious specifier is supported by several studies [51–55], it has to be pointed out that at least some of these studies [51,52] did not assess all the DSM-5 criteria of the anxious specifier. Other authors [53] noted that some of the considered proxy items may not have been accurate representations of a DSM-5 criterion. Zimmerman et al. [50], evaluating the validity of the DSM-5 anxious specifier through an ad-hoc interview - the DSM-5 Anxious Distress Specifier Interview (DADSI) - found that the majority of patients suffering from major depression fulfill the criteria for the anxiety specifier showing high scores on anxiety and depression measures, confirming the utility of such specifier. Thus, the debate about the clinical utility of this specifier is still ongoing, and further studies are needed.

As regards the "with mixed features" specifier, a high consensus was reached for statements dealing with its utility for selecting the pharmacological treatment and for the differential diagnosis between unipolar and bipolar depression. The introduction of "mixed features" in the DSM-5 has replaced the "mixed episode", highlighting the shift toward a more dimensional approach to mental disorders. Within a major depressive disorder, the specifier "with mixed features" can be coded by the presence of at least three out of seven hypomanic symptoms (i.e., elevated mood, inflated self-esteem, pressured speech, racing thoughts, goal-directed activity, involvement in risky activities, and decreased need for sleep) are present [56]. However, it has been proposed that mixed depression is a distinctive condition in the spectrum of mood disorders, and therefore this specifier should be routinely used in clinical practice to differentiate this subtype of depressive disorder from other forms. Some authors have proposed that "depression with mixed features" should be replaced by "agitated depression" [57–60], highlighting the continuum from unipolar to bipolar disorders, with relevant implications for the development of the appropriate treatment plan. This view is shared also from the majority of experts involved in the Delphi panel, confirming the need to broaden the diagnostic depressive categories in order to better address patients' clinical needs.

Experts reported a strong consensus on the relevance of the "with melancholic features" specifier for identifying people suffering from the most severe forms of depression, including those with marked anhedonic features, significant suicidal risk or "difficult to treat" depression. The melancholic specifier is one of the oldest specifiers, linked to the conceptualisation of depression from centuries ago and first introduced as operational criterion in DSM-III in 1980s [61]. This specifier has been introduced to identify a more homogeneous group of individuals suffering from depression, but the discussion on its validity is still ongoing [62]. Although the DSM-5 states that this specifier can help to identify homogeneous subgroups of individuals, Friedl et al. [63] pointed out that this seems highly unlikely, given that more than 340.000 unique profiles are possible. Moreover, in line with studies failing to identify specific antidepressants more efficacious than others for the treatment of specific characteristics of depressive episodes [64–67], a negative agreement was reached on the utility of the melancholic specifier for the differential diagnosis between unipolar and bipolar depression and for supporting the choice of the appropriate pharmacological treatment.

The highest no consensus rate was reached for the "with atypical features" specifier compared to all other statements included in the present Delphi survey. This finding confirms the complexity of the concept of atypical depression, being the depressive subtype with the highest prevalence of axis 1 comorbidities [68,69]. The concept of atypical depression has evolved throughout the years and, starting from the DSM-5, this specifier is now included in both chapters dealing with depressive and bipolar disorders. The prevalence rates of depression with atypical features are variable, depending on criteria, methodologies, and settings. As pointed out by Parker [70], the definition of atypical features specifier for a major depressive episode is problematic. As suggested by earlier descriptions of atypical depression, certain expressions of anxiety may have primacy, while some other clinical features may be considered a homeostatic adaptation to other primary

symptoms. Moreover, a recent study by Lorenzo-Luaces et al. [41] found that differences between atypical and non-atypical depression are smaller than what would be expected by chance.

An almost complete agreement was found for statements dealing with the "with psychotic features" specifier, confirming its clinical utility for identifying a specific subset of patients. In particular, patients suffering from psychotic depression are significantly different from non-psychotic depressed patients in terms of clinical characteristics, medical history, treatment response pattern and neurobiological data [71], and thus would require a different treatment plan, which might include also second or third generation antipsychotics.

A positive agreement was reached regarding the clinical utility of the specifier "with catatonic features". Experts involved in the Delphi survey support the idea that the changes introduced by DSM-5 on this specifier should be considered "sufficient to significantly improve clinical diagnosis" [61]. Moreover, this specifier can be useful to describe a specific and unique subtype of depression requiring ad-hoc treatment. As Tandon [72] pointed out, the decision to keep catatonia as a specifier and not as an independent diagnosis is confirmed by the fact that treatments including benzodiazepines and ECT are more effective when catatonia occurs in the context of depression in contrast to other disorders [73,74].

The following limitations must be acknowledged. Firstly, the invited experts were all from Italy, a country with a longstanding tradition in phenomenology and classification of mental disorders [75]. Moreover, participants were expert psychiatrists working in university settings. Therefore, our findings should be replicated involving a larger panel of experts, coming from countries with different backgrounds and traditions, in order to identify any difference in relation to the country region. Second, the Delphi method is used to analyse and summarize experts' opinions, but not necessarily a consensus is reachable for all statements due to controversies in the field. Finally, although Delphi method is a valid and reliable approach for summarizing strength of scientific evidence, it should be confirmed by more rigorous methods, such as systematic reviews and meta-analyses.

5. Conclusions

MDD is a common severe mental disorder, associated with high levels of personal and societal burden [76–78]. The clinical manifestations of depressive disorders can be very heterogeneous and therefore it is necessary to use classification systems which acknowledges such complexity [79,80].

To our knowledge, this is the first Delphi-based consensus survey on the clinical utility of DSM-5 specifiers for depressive disorder, involving experts in affective disorders. Our findings reveal a large agreement among the expert group of Italian specialists on the majority of the considered areas. In particular, the level of agreement was maximum for the clinical utility of specifiers in ordinary practice; the usefulness of "with anxiety features" for selecting a pharmacological treatment including an antidepressant drug with anxiolytic properties; the relevance of "with psychotic features" specifier for characterizing a specific subgroup of most severe patients with depression was clearly highlighted. As for the other specifiers, further studies are needed in order to understand whether they are useful in clinical practice and their adoption should be kept in the future revisions of the manual or if the categorical approach should be replaced by the dimensional one.

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Andrea Fiorillo: Writing – original draft, Data curation, Conceptualization. **Umberto Albert:** Writing – review & editing, Conceptualization. **Bernardo Dell'Osso:** Writing – review & editing, Methodology. **Maurizio Pompili:** Writing – review & editing, Data curation, Conceptualization. **Gabriele Sani:** Writing – review & editing, Resources. **Gaia Sampogna:** Writing – original draft, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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