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Research report

Phenomenology of manic episodes according to the presence or absence of depressive features as defined in *DSM*-5: Results from the IMPACT self-reported online survey

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ABSTRACT

Background: The aim of this study was to describe the phenomenology of mania and depression in bipolar patients experiencing a manic episode with mixed features as defined in the new *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*-5).
Methods: In this multicenter, international on-line survey (the IMPACT study), 700 participants completed a 54-item questionnaire on demographics, diagnosis, symptomatology, communication of the disease, impact on life, and treatment received. Patients with a manic episode with or without *DSM*-5 criteria for mixed features were compared using descriptive and inferential statistics.
Results: Patients with more than 3 depressive symptoms were more likely to have had a delay in diagnosis, more likely to have experienced shorter symptom-free periods, and were characterized by a marked lower prevalence of typical manic manifestations. All questionnaire items exploring depressive symptomatology, including the *DSM*-5 criteria defining a manic episode as "with mixed features", were significantly overrepresented in the group of patients with depressive symptoms. Anxiety associated with irritability/agitation was also more frequent among patients with mixed features.
Limitations: Retrospective cross-sectional design, sensitive to recall bias. Two of the 6 *DSM*-5 required criteria for the specifier "with mixed features" were not explored: suicidality and psychomotor retardation.
Conclusions: Bipolar disorder patients with at least 3 depressive symptoms during a manic episode self-reported typical symptomatology. Anxiety with irritability/agitation differentiated patients with depressive symptoms during mania from those with "pure" manic episodes. The results support the use of *DSM*-5 mixed features specifier and its value in research and clinical practice.

1. Introduction

Depressive symptomatology concomitant to a manic episode in bipolar disorder (BD) (also termed mixed, depressive, or dysphoric mania) constitutes a severe form of the disorder that is commonly seen in daily practice (Vieta and Valenti, 2013). At the epidemiological and clinical level, compared to pure manic episodes, mania with concomitant depressive symptoms occurs at a younger age, and is associated with more frequent episodes of longer duration, more frequent relapses, lower interepisode intervals, longer time to achieve symptomatic remission, and higher rates of suicide and comorbid conditions such as substance abuse (Swann et al., 2013; Vieta and Valenti, 2013). Moreover, compared with patients with pure manic episodes, individuals with depressive features have a poorer response to treatment, a poorer long-term prognosis, more often require combination therapy, and are at greater risk of mood-switching following antimanic treatment (Swann et al., 2013; Vieta and Valenti, 2013).

The diagnosis and classification of mixed manic states is a matter of debate, and several different criteria have been proposed; some are based on a broad dimensional or intermediate categorical perspective to better account for the presence of subsyndromal symptomatology, while others have a more strict bidimensional approach, as used in official diagnostic classification

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systems such as the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*), *or the Classification of Mental and Behavioral Disorders* (*ICD*) (Vieta and Valenti, 2013). In the new *DSM*-5 edition, a mixed-categorical-dimensional definition has been adopted, and mixed episodes, defined in previous versions as the co-occurrence of full mania and depression episodes for ≥ 1 week (American Psychiatric Association, 2000), has been removed. Instead, a "with mixed features" specifier will now be used for a manic episode presenting with at least 3 of the following symptoms of the opposite polarity: (1) prominent dysphoria or depressed mood, (2) diminished interest or pleasure in all, or almost all, activities, (3) psychomotor retardation nearly every day, (4) fatigue or loss of energy, (5) feelings of worthlessness or excessive or inappropriate guilt, and (6) recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

The assessment and quantification of a possible depressive component during mania in clinical research will improve accuracy of diagnosis and classification, hopefully leading to a better tailored treatment, better prognosis and improved functioning. There are several options (not mutually exclusive) to identify the depressive dimension associated with mania. These include the use of: (1) classical scales to rate the intensity of the depressive symptomatology (e.g. the Hamilton Depression Rating Scale, or the Montgomery-Åsberg Depression Rating Scale), (2) the score in the number of symptoms present in a checklist of prominent depressive symptoms (e.g. Cincinnati or Vienna criteria) (Akiskal, 1992; McElroy et al., 1992; Swann et al., 2013), (3) the assessment of the presence of specific temperament characteristics (e.g. Duke/ROC, or Pisa-San Diego criteria) (Cassidy et al., 2000; Perugi et al., 1997), (4) observer-rated scales designed to measure both manic and depressive symptoms (e.g. the Bipolar Inventory of Symptoms Scale) (Bowden et al., 2007), and/or (5) self-completed instruments which can also simultaneously capture symptoms of both polarities (e.g. the Internal State Scale, the Multiple Visual Analog Scale of Bipolarity, or the Self-Report Manic Inventory)(Azorin and Hantouche, 2001; Picardi, 2009).

Although the capability of patients with manic symptoms to make judgments on their symptoms has been questioned, the self-assessment of mania is reliable and valid even in patients with psychotic features or limited insight (Altman, 1998). It has also been demonstrated that patients with manic episodes consistently report dysphoric symptoms through self-rated depression scales, with results highly concordant with observer-rated scales (Cassidy et al., 2009). Most importantly, the differences in self-reported depressive symptoms can discriminate pure from mixed states in the acute phase of the illness (Akiskal et al., 1998; Azorin et al., 2008; Cassidy et al., 2009; Hantouche et al., 2001).

The aim of this study was to describe the specific phenomenology and the frequency of manic and depressive symptoms in bipolar patients experiencing manic episodes with depressive features as defined in the new *DSM*-5. We used a subset of results specifically related to the presence of depressive symptoms during a manic phase obtained from a qualitative and quantitative online survey (IMPACT), designed to retrospectively assess how bipolar disorder I (BDI) impacts patients' lives and their priorities for successful treatment.

2. Methods

2.1. Survey and participants

The study was conducted in Australia, Canada, France, Germany, Italy, Spain, and the UK between 26th March and 31st July 2012. An online questionnaire (IMPACT) was used to screen patients and collect qualitative and quantitative data. Access to the survey was secure, ensuring the anonymity of the participants. Individuals were recruited through consumer panels, via psychiatrists, or patient organizations (Fig. 1). Individuals aged 18–65 years who gave their consent by answering a specific question on their willingness to participate, were subsequently asked to complete an online screening form. Participants were eligible if they were diagnosed with BDI more than 12 months before participating; had an episode of mania ever that caused significant distress or greatly impaired their work, family or social life; had an increase in at least 5 out of 20 statements on affective symptoms during a period of mania; were in meaningful remission (no affective symptoms for 3–4 weeks minimum); and were treated with at least one medication indicated for BDI in the preceding 2 years. A quota sampling procedure was applied, with limits in the following categories: (1) up to 55% of males or females, (2) up to 25% of all participants in each age group (18–25, 26–36, 36–45, 46–55, and 56–65 years), (3) a maximum of 25% of all participants diagnosed between 12 and 24 months before the survey, a maximum of 35% diagnosed between 2 and 10 years before the survey, and a maximum of 40% of those diagnosed more than 10 years previously, and (4) a maximum of 50% of participants with predominant depressive polarity. Eligible participants were thereafter routed to the second part of the IMPACT questionnaire, containing sets of questions on demographics (work and marital status), diagnostic process and time from onset of symptoms to diagnosis, communicating BD to family and others, impact of the disease (work life, personal life, relationships, and sleep patterns), presence of depressive symptoms during a manic phase, periods of mania and hospitalizations, and the outcome of treatment. Per country 100 patients participated and all participants fully completed the questionnaire.

2.2. Questions related to mania and depression

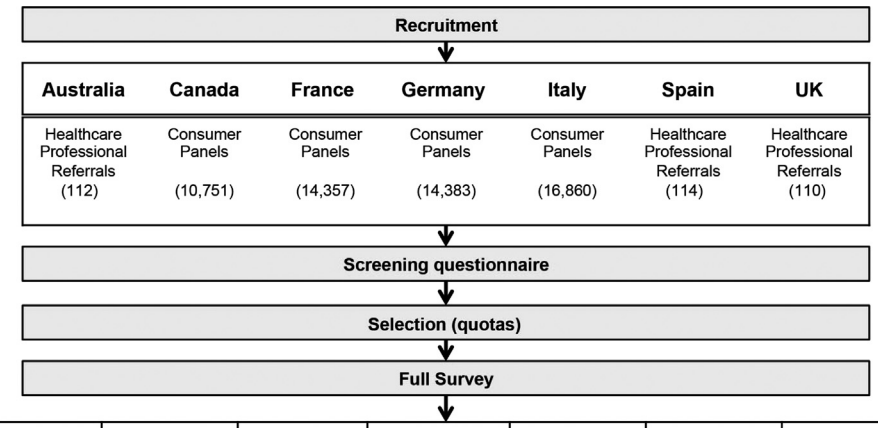
The questionnaire contained 15 questions related to manic symptoms, 13 related to depressive symptoms, one on anxiety or worry, and one on irritability or agitation (Supplementary Material, and Table 2). Seven out of the 13 questions on depressive symptomatology matched 4 out of the 6 *DSM*-5 criteria for a manic episode with mixed features: depressed mood, decreased interest or pleasure (presence of lack of interest/lethargy and/or decreased sense of pleasure), feelings of guilt or worthlessness (feelings of guilt and/or feelings of low self-esteem and/or lack of confidence), and lack of energy (decrease in energy levels). No data were obtained for the 2 additional *DSM*-5 criteria: suicidal thoughts and psychomotor retardation.

Patients reporting <3 depressive symptoms (the "M w/o DS" group), were defined as having a pure manic episode; patients reporting ≥ 3 depressive symptoms (the "M with DS" group) were defined as having a manic episode with mixed features.

2.3. Statistical Analyses

Patients who experienced <3 depressive symptoms (M w/o DS) were compared with patients who experienced ≥ 3 depressive symptoms (M with DS). This cut-off was chosen for the current study because it has been previously proposed to be a practical criterion in the clinical setting to diagnose mixed mania (McElroy et al., 1992; Swann et al., 2013). Descriptive statistics comprised the total and frequency of responses. Statistical comparisons between the two groups were made using the Chi-square test. All of the Chi-square statistics used 2 by 2 tables with one degree of freedom. No correction was applied for multiple testing, and p values less than 0.05 were considered to be significant. Odds ratios and 95% confidence intervals (CIs) were calculated as

A



	Australia	Canada	France	Germany	Italy	Spain	UK	Total, n (%)
Total (n)	100	100	100	100	100	100	100	700
Mania w DS	37	36	53	43	54	14	38	275 (39%)
Mania w/o DS	63	64	47	57	46	86	62	425 (61%)

B

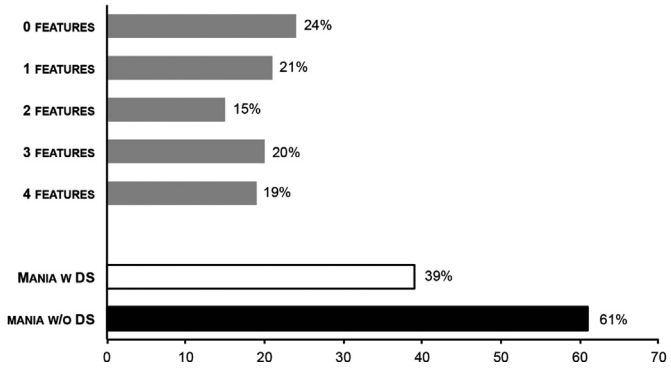


Fig. 1. Description of the IMPACT study methods and sampling for the present study for each country (A), and graphic representation of the distribution of patients according to the number of depressive features reported during a past manic episode (B).

a function of the impact of the presence of depressive symptoms (M with *DSM* vs. without DS). Results are presented as comparisons of the M with DS group vs. the M w/o DS group unless otherwise specified in the text.

3. Results

3.1. Demographic characteristics

Out of the 56,687 subjects initially screened, 700 subjects (100 per country) completed the IMPACT questionnaire (Fig. 1A). During a past manic episode, 39% ($n=275$) of patients reported ≥ 3 *DSM*-5 depressive symptoms (M with DS), and 61% reported <3 (M w/o DS) ($n=425$) (Fig. 1B). Differences in age and gender frequency between groups were not significant. There were more females in the M with DS group, but this difference was not significant (40% vs. 47%, $p=0.07$). Subjects in the M with DS group were less likely to be retired than those in the M without DS group ($p=0.02$; OR=0.59, 95% CI=0.4–0.9); differences regarding relationship status were not significant.

3.2. Psychiatric history

Patients in the M with DS group were more likely to have been diagnosed with BDI in recent years (in the last 5 years), and less likely than those in the M w/o DS group to have been diagnosed 6–10 years ago (19.6% vs. 28.7%; $p=0.007$) (Table 1). A diagnosis more than 10 years ago was equally likely in both groups.

Patients in the M with DS group were more likely to have depressive symptoms with some manic symptoms at diagnosis (46.9% vs. 28.9%; $p<0.001$), and were less likely to have experienced only manic symptoms (7.6% vs. 28.2%; $p<0.0001$).

Individuals in the M with DS group were more likely to have experienced shorter periods free of symptoms (3–4 weeks) than those in the M w/o DS group (44.7% vs. 20.5%; $p<0.0001$).

3.3. Misdiagnosis before BDI diagnosis

Nearly half of the patients in both groups were initially diagnosed with another condition: 39% of those in the M with DS group, and 43% of those in the M w/o DS group (Table 1). Patients in the M with DS group were significantly more frequently misdiagnosed as having insomnia (46.7% vs. 27.9%; $p<0.0001$), but were less likely than those in the M w/o DS group to be misdiagnosed with a major depressive episode (MDE) or major depressive disorder (MDD) (22.4% vs. 34.4%; $p=0.02$).

3.4. Manic symptoms

Out of the 15 manic symptoms assessed, 11 were more likely to be experienced by patients in the M w/o DS group (Table 2 and

Table 1
Psychiatric history and illness course of IMPACT study respondents according to the presence of depressive symptoms.

	Mania with DS $n=275$	Mania w/o DS $n=425$	p Value[a]	Odds ratio (95% CI)
Length of time since diagnosis, *n* (%)				
12–24 months	56 (20.4)	46 (10.8)	<0.0001	2.11 (1.38–3.22)
2–5 years	89 (32.4)	106 (24.9)	0.03	1.44 (1.03–2.01)
6–10 years	54 (19.6)	122 (28.7)	0.007	0.61 (0.42–0.87)
11–20 years	51 (18.5)	98 (23.1)	NS	
21 or more years	25 (9.1)	53 (12.5)	NS	
Symptoms at diagnosis, *n* (%)				
Manic only	21 (7.6)	120 (28.2)	<0.0001	0.21 (0.13–0.34)
Primarily manic, some depressed	88 (32.0)	134 (31.5)	NS	
Primarily depressed, some manic	129 (46.9)	123 (28.9)	<0.0001	2.17 (1.58–2.98)
Depressive only	36 (13.1)	47 (11.1)	NS	
Longest period without BDI symptoms since diagnosis, *n* (%)				
3–4 weeks	123 (44.7)	87 (20.5)	<0.0001	3.14 (2.25–4.39)
5–6 weeks	48 (17.5)	58 (13.6)	NS	
6 weeks or longer	104 (37.8)	280 (65.9)	<0.0001	0.31 (0.23–0.42)
Misdiagnosis, *n* (%)				
Total	107 (38.9)	183 (43.0)		
Insomnia	50 (46.7)	51 (27.9)	0.001	2.27 (1.38–3.74)
Major depression or major depressive disorder	24 (22.4)	63 (34.4)	0.02	0.55 (0.33–0.90)
Attention deficit hyperactivity disorder	25 (23.4)	31 (16.9)	NS	
Psychosis	23 (21.5)	41 (22.4)	NS	
Schizophrenia	19 (17.8)	22 (12.0)	NS	
Schizoid personality disorder	16 (15.0)	15 (8.2)	NS	
Anxiety or generalized anxiety disorder	7 (6.5)	9 (4.9)	NS	
Borderline personality disorder	5 (4.7)	10 (5.5)	NS	
Manic depression	3 (2.8)	2 (1.1)	NS	
Post-partum depression	0 (0.0)	1 (0.5)	NS	
Obsessive–compulsive disorder	2 (1.9)	2 (1.1)	NS	
Anorexia	1 (0.9)	2 (1.1)	NS	
Schizoaffective disorder	0 (0.0)	3 (1.6)	NS	

NS: non-significant.

[a] Mania with DS vs. mania w/o DS.

Fig. 2), and only physical aggression and abusive behavior towards others were more frequently reported by individuals in the M with DS group (35.6% vs. 23.5%, and 41.5% vs. 32.9%, respectively; $p=0.001$ and $p=0.02$, respectively).

3.5. Depressive symptoms

Feeling depressed during an episode of mania was reported by 64% of the patients (46.3% in the M w/o DS vs. 94.5% in the M with DS groups). All of the 13 depressive symptoms assessed were significantly more represented among the patients in the M with DS group (Table 2 and Fig. 2B). Depressive symptoms were grouped to match 4 out of the 6 *DSM*-5 definitions of mania with mixed features, and all of them were found to be significantly overrepresented in the group M with DS (all items $p<0.001$) (Table 2 and Fig. 2C).

3.6. Anxiety and irritability or agitation

A lower proportion of individuals in the M with DS group reported feelings of irritability and agitation than of those in the M w/o DS group (7.6% vs. 38.1%; $p<0.0001$), but they were more likely to feel anxious or worried (14.2% vs. 6.8%; $p=0.001$). Moreover, more patients in the M with DS group had symptoms of anxiety and irritability associated with agitation (72.4% vs. 27.1%; $p<0.0001$) (Table 2 and Fig. 2D).

4. Discussion

We performed an online patient survey to describe the phenomenology of a manic episode with mixed features as newly operationalized in *DSM*-5. Two-third (64%) of patients reported feeling depressed when experiencing a manic episode. The self-reported frequency of ≥ 3 concomitant depressive symptoms during a manic episode in our study was 39%, which is in accordance with the overall 31% reported using broader criteria than those of official classification systems (*ICD*-10 and *DSM*-IV-TR) (McElroy et al., 1992), and close to the 23% prevalence described based on clinician's judgment (Vieta and Morralla, 2010).

Patients with DS were more likely than patients without DS to have been diagnosed less than 5 years ago. This could be related to the known complex phenomenology that accompanies this disorder, which is associated with a delay in its clinical recognition and classification (Akiskal et al., 1998; Hantouche et al., 2006; McElroy, 2008). We also recorded a high rate of misdiagnosis (39% in the case of mania with DS, and 43% in the case of mania without DS), which are in accordance with previously reported rates of incorrectly diagnosed BD (Keck et al., 2008; Zimmerman, 2010). Patients without DS were more frequently misdiagnosed as having a MDE or MDD than those with DS. Patients with mixed states have been shown to come more frequently from cohorts with mixed onset, compared to patients with pure mania (Perugi et al., 2000), highlighting the strong correlation between polarity onset and predominant polarity during the illness (Baldessarini et al., 2012; Daban et al., 2006). In line with this, patients with pure mania may have a more frequent manic onset; however as manic onset appears to be much less frequent than depressive onset (Keck et al., 2008; Perugi et al., 2000), it is likely that patients pure manic symptoms recruited in this study could come from cohorts with depressive onset. In this regard, it was found in a recent study, that patients with depressive onset were more often misdiagnosed as major depressive disorder, compared with patients with mixed onset (Azorin et al., 2011). Patients with DS had a 2 fold higher probability of having been diagnosed with insomnia than patients without DS, a fact that to our knowledge

Table 2
Self-reported symptoms of IMPACT study respondents according to the presence of depressive symptoms.

	Mania with DS $n=275$	Mania w/o DS $n=425$	p Value[a]	Odds ratio (95% CI)
Manic symptoms, *n* (%)				
Over-activity	179 (65.1)	367 (86.4)	< 0.0001	0.29 (0.20–0.43)
Excessive behavior	160 (58.2)	303 (71.3)	< 0.0001	0.56 (0.41–0.77)
Risk taking behavior	137 (49.8)	250 (58.8)	0.02	0.69 (0.41–0.94)
Impulsive behavior	210 (76.4)	344 (80.9)	NS	0.76 (0.51–1.10)
Overly sociable	82 (29.8)	259 (60.9)	< 0.0001	0.27 (0.38–0.53)
Physical aggression	98 (35.6)	100 (23.5)	0.001	1.80 (1.98–2.51)
Abusive towards others	114 (41.5)	140 (32.9)	0.02	1.74 (1.29–1.97)
Promiscuity	55 (20.0)	133 (31.3)	0.001	0.55 (0.38–0.79)
Rapid speech	155 (56.4)	324 (76.2)	< 0.0001	0.40 (0.38–0.56)
Talking too much	158 (57.5)	326 (76.7)	< 0.0001	0.41 (0.29–0.57)
Racing thoughts	224 (81.5)	369 (86.8)	NS	0.67 (0.29–1.1)
Feeling happy/euphoric	122 (44.0)	360 (84.7)	< 0.0001	0.14 (0.2–0.4)
Feelings of superiority	78 (28.4)	277 (65.2)	NS	0.21 (0.29–1.46)
Feeling sexual	63 (22.9)	201 (47.3)	< 0.0001	0.33 (0.15–0.46)
Not feeling the need to sleep	145 (52.7)	347 (81.6)	< 0.0001	0.25 (0.18–0.35)
Depressive symptoms, *n* (%)				
(*DSM-5 mixed features specifier*)				
Depressed mood	260 (94.5)	188 (46.3)	< 0.0001	20.09 (11.53–35.04)
Decreased interest/pleasure				
Lack of interest/lethargy	187 (68.0)	17 (4.0)	< 0.0001	51.0 (29.50–88.16)
Decreased sense of pleasure	178 (64.7)	66 (15.5)	< 0.0001	9.98 (6.96–14.32)
Feelings of guilt/worthlessness				
Feelings of guilt	156 (56.7)	50 (11.8)	< 0.0001	9.83 (6.73–14.37)
Feelings of low self-esteem	196 (71.3)	41 (9.6)	< 0.001	23.24 (15.35–31.18)
Lack of confidence	196 (71.3)	22 (5.2)	< 0.0001	45.45 (27.50–75.11)
Lack of energy				
Decrease in energy levels	194 (70.5)	21 (4.9)	< 0.0001	46.08 (27.68–76.70)
Other symptoms, *n* (%)				
Not wanting to socialize	171 (62.2)	53 (12.5)	< 0.0001	11.5 (7.91–16.82)
Low sex drive	125 (45.5)	23 (5.4)	< 0.0001	14.56 (8.99–23.60)
More need for sleep than usual	127 (46.2)	27 (6.4)	< 0.0001	12.65 (8.01–19.96)
Difficulty focusing	227 (82.5)	320 (75.3)	0.02	1.55 (1.06–2.27)
Not remembering things	168 (61.1)	202 (47.5)	< 0.0001	1.73 (1.27–2.36)
Difficulty making decisions	178 (64.7)	171 (40.2)	< 0.0001	2.73 (1.99–3.73)
Feeling anxious or worried only	39 (14.2)	29 (6.8)	0.001	2.26 (1.36–3.75)
Feeling irritable or agitated only	21 (7.6)	162 (38.1)	< 0.0001	0.13 (0.08–0.22)
Feeling anxious or worried and irritable or agitated	199 (72.4)	115 (27.1)	< 0.0001	7.06 (5.02–9.92)

[a] Comparison of Mania with DS vs. mania w/o DS patients.

has not been described before. The results are in agreement with previous observations of a shorter average total sleep time associated with severity of mania, and a greater variability in sleep time associated with a greater severity of both mania and depressive symptoms (Gruber et al., 2011), which could ultimately lead to a frequent misdiagnosis of insomnia in patients with DS.

At diagnosis, patients with DS had primarily depressive symptoms with some manic symptoms (46.9% M with DS vs. 28.9% M w/o DS). Most of the patients without DS had a clinical presentation with only manic symptoms (28.2% M w/o DS vs. 7.6% M with DS). A substantial proportion of patients in the group without DS (32%), however, reported primarily manic, but some depressive symptoms too, which could be explained by a contamination of this group with subjects having only 1 or 2 DS. This stresses the need to explore the presence of depressive symptoms in patients whose initial presentation is apparently "pure manic" (Cassidy and Carroll, 2001; Cassidy et al., 1998b).

We found that patients with DS self-reported significantly shorter periods free of symptoms, which is in accordance with previous studies showing that mixed patients have a lower proportion of inter-episodic remission (Azorin et al., 2008; Perugi et al., 1997).

As for the phenomenology of mania, patients with DS were characterized by a marked lower prevalence of typical manic manifestations. It is noteworthy the significant lesser over-activity, euphoria, grandiosity, overly sociability, and decreased need to sleep. These manic symptoms have been consistently found to be less represented in patients with mixed features (Cassidy and Carroll, 2001; Cassidy et al., 1998a, 1998b; Goldberg et al., 2000; Hantouche et al., 2006), although it has been proposed that, being relatively infrequent and less evident, they might be of limited utility when trying to discern a pure manic from mixed episodes features (Goldberg et al., 2000). Two manic symptoms were found to be significantly more frequently self-reported by the group with DS: physical aggression and being abusive towards others. Aggression is a feature of BD that develops in the context of irritability, it is reported in subjects during acute episodes or without current mood symptoms, and has a frequency similar in acute manic and mixed episodes (Ballester et al., 2012; Latalova, 2009). Trait aggression is significantly predicted by the presence of a comorbid borderline personality disorder, and by the severity of current manic and depressive symptomatology (Garno et al., 2008). It is not surprising then that the group of patients with DS, who probably have more severe symptoms and feelings of frustration and rage, reported higher rates of aggression in our study.

Regarding the phenomenology of depression, we found that 4 out of the 6 new *DSM*-5 criteria were significantly different between groups. Although this difference was expected because patients were grouped based on the number of depressive symptoms, this preliminarily confirms that a threshold of 3 depressive symptoms has discriminating value, which is in accordance with previously proposed clinical criteria to identify and diagnose mixed manic episodes (McElroy et al., 1992; Swann et al., 2013). Nevertheless, these 3 depressive symptoms are not unique discriminators, as other symptoms were shown to also be able to differentiate groups. Thus, the presence of other or additional

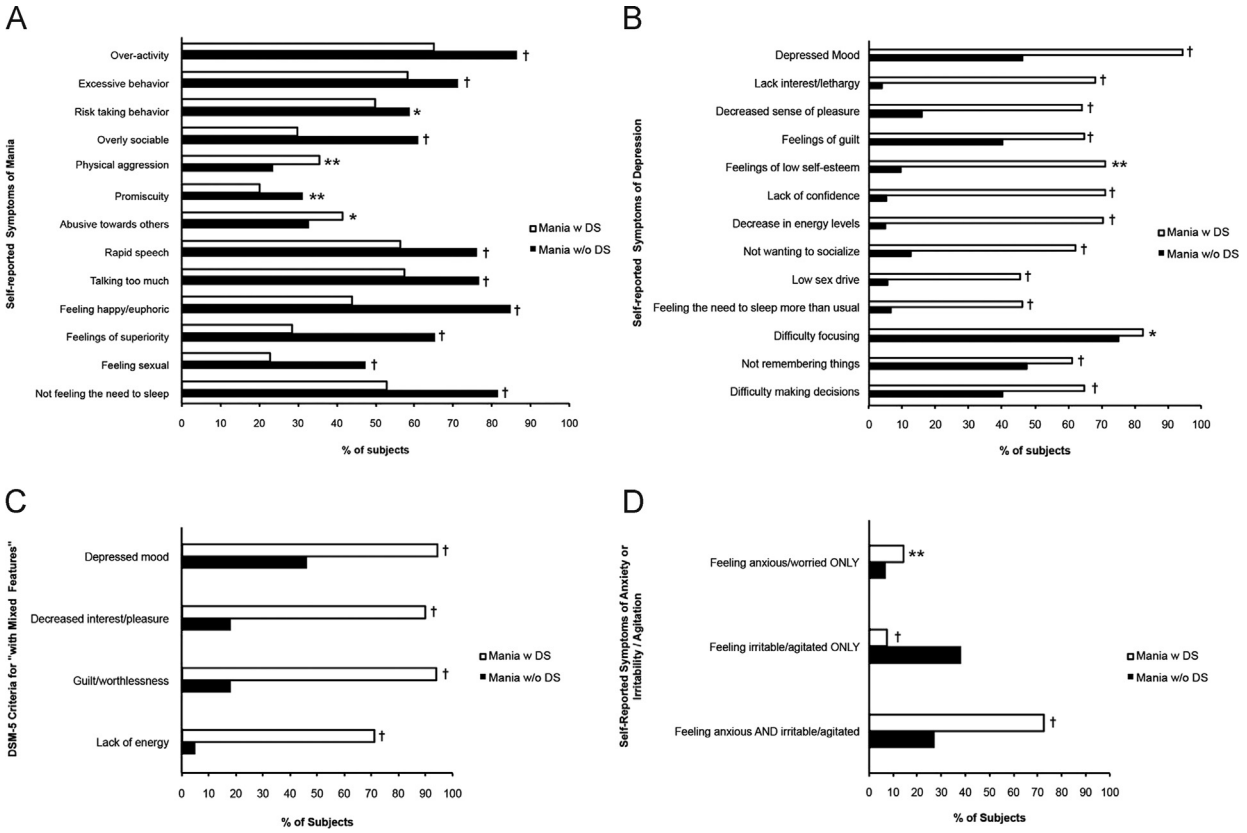


Fig. 2. Frequency of respondents ($n=700$) who, during a past manic episode, self-reported manic symptoms (A), depressive symptoms (B), depressive symptoms as defined by the "mixed features specifier" in *DSM*-5 (C), and symptoms of anxiety or irritability associated with agitation (D). *$P<0.05$ Mania with DS versus Mania w/o DS; **$P<0.001$ Mania with DS versus Mania w/o DS; †$P<0.0001$ Mania with DS versus Mania w/o DS.

depressive symptoms could also be of clinical value when attempting to differentiate pure from manic episodes with mixed features.

Depressed mood, anxiety, excessive guilt, and increased suicidality have been identified as core depressive symptoms in the context of mixed states in factor and cluster analyses (Akiskal et al., 1998; Cassidy and Carroll, 2001; Cassidy et al., 1998a, 1998b). In the present study, both depressed mood and feelings of guilt were found to be able to differentiate between the two groups of patients, but the presence of suicidal thoughts and behaviors, which is also one of the required criteria of *DSM*-5, was not assessed in the survey. In fact, *DSM*-5 differentiates between two new specifiers: the *mixed features* specifier, as analyzed in this study, and the *suicidal risk* specifier, which should be assessed separately. The IMPACT survey also assessed non-mood symptoms, including anxiety, agitation, and irritability, which are prominent components of mixed manic states (Vieta and Valenti, 2013). Factor analyses on the symptom structure of mania have consistently found that anxiety has strong positive loading on the depression factor (Cassidy, 2010). Moreover, anxiety correlates with the presence and severity of depressive symptoms in patients with mixed mania (Azorin et al., 2009; Swann et al., 2009) and is associated with poor outcome (Gonzalez-Pinto et al., 2012). This is in accordance with the results of the present study, where the frequency of anxiety was higher among patients with DS, and with the suggestion made by others that it should be considered a specific symptom (excluded from the *DSM*-5 needed depressive features) that is also able to discriminate between the two states (Cassidy, 2010; Pacchiarotti et al., 2013). Irritability has also been consistently identified as being part of the symptom structure of mixed mania (Swann et al., 2013), and reported to be more prevalent among patients with more than 2 or 3 depressive symptoms (Cassidy et al., 1998a; Goldberg et al., 2000; Hantouche et al., 2006). Although feelings of only agitation or irritability were more common among patients without DS in our cohort, the presence of both anxiety and irritability or agitation was 5–9 folds more probable to be self-reported by patients with DS. The combination of anxiety and irritability or agitation during a manic episode could be used as a relevant discriminator for the presence of depressive symptoms.

Finally, one interesting finding in the IMPACT study is that patients with DS significantly reported having more difficulty remembering things, focusing, and making decisions than patients without DS. Although differences in neuropsychological deficits between patients with pure manic symptoms and patients with depressive symptoms have rarely been explored, patients with mixed episodes as defined by *DSM*-III-R criteria were reported to perform more poorly in overall attention tasks than patients with pure manic episodes (Sax et al., 1995), and subthreshold depressive symptoms have been reported to influence neurocognitive performance (Bonnin et al., 2012). There are a number of strengths and limitations to the study. A strength is that the participants in the survey may be representative of the overall BDI population, as they were selected to match similar demographic characteristics and were not obtained from tertiary centers, as in many other studies (Vieta, 2013). Besides, the study obtained a large sample size of patients that were engaged across seven different countries, which probably allows extrapolation of the results within a larger framework of countries. Nevertheless, we do acknowledge a possible sample bias, as the online survey was based on a voluntary response, and there is no information on the clinical profile of those who refused to participate. Moreover, the study was based on a retrospective cross-sectional design and subject to recall bias, and warrants a longitudinal validation. Finally, the respondents are limited to a population of euthymic outpatients, which might also have biased the sample by excluding subjects

with more severe affective symptomatology. However, our results in general are in agreement with other community surveys that enrolled patients during the acute phase (Akiskal et al., 1998; Azorin et al., 2008; Hantouche et al., 2006, 2001), and with the only one that included both inpatients and outpatients (Azorin et al., 2009). Moreover, it has been reported that the concordance between observer vs. self-rated scales increases with the patient's symptomatological improvement (Moller, 2000). Thus, the fact that our population self-reported their symptoms during euthymia might have not negatively impacted the results. Our results are also concordant with surveys that used exclusively self-rated scales (Hantouche et al., 2001), or a combination of clinician and self-reported instruments (Akiskal et al., 1998; Azorin et al., 2008; Hantouche et al., 2006, 2001).

The findings of the IMPACT survey show that the self-rated retrospective assessment of symptoms during mania is feasible, and could be a helpful for clinicians to assess mixicity. Actually, both prospective and retrospective self-ratings to dimensionally assess mania and depression have shown its reliability and validity, and are being used in naturalistic studies such as the Stanley Foundation Bipolar Network (Post et al., 2001) and the WAVE-bd study (Vieta et al., 2013). Finally, the results of the survey preliminarily show that a threshold of 3 depressive symptoms during a manic episode as operationalized in the new *DSM*-5 can be used to identify mixed vs. non-mixed patients. The 3-symptom threshold should now be also validated for depressive episodes with mixed features, as proposed in *DSM*-5.

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Conflict of interest

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2013.12.031.

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