

## Symptoms of Anxiety and Irritability in Patients with Major Depressive Disorder

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### Abstract

**Background:** Anxiety and irritability often coexist in patients with major depressive disorder (MDD). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) added criteria for an anxious distress specifier for MDD. This study aimed at understanding the various components of anxiety and irritability, their impact, and relationships among them in MDD; and the association of anxious distress and irritability with treatment response.

**Methods:** Focus groups were conducted with patients with MDD reporting symptoms of anxiety, irritability, agitation, and/or aggression. Clinical study data were pooled from open-label antidepressant treatment (ADT) phases of seven studies in patients with MDD and a history of inadequate response for the current depressive episode to one to three ADTs (N = 5,182). Post hoc criteria using study measures were applied to identify patients with symptoms of anxious distress and irritability. ADT response rates were compared for patients with and without anxious distress and irritability.

**Results:** Symptoms of anxiety and irritability frequently coexisted for the focus group participants who often described symptoms of anxious distress (e.g., nervous, tense, restless, worry, fear, out of control, acting out). In the clinical studies, approximately 50% of patients with inadequate response to ADTs presented with symptoms of anxious distress and irritability. The presence of anxious distress was associated with lower ADT response rates.

**Conclusions:** Various anxiety symptoms, including those comprising anxious distress, are prevalent and meaningful in depression, and frequently associated with irritability. Symptoms of anxious distress are associated with a decreased likelihood of ADT response.

**Keywords:** Anxiety; Emotion; Psychiatric disorders; Psychopharmacology

### Introduction

Major depressive disorder (MDD) is characterized by several diagnostic or core symptoms and feelings such as sadness, loss of interest or pleasure in usual activities, sleep and/or appetite disturbances, and fatigue [1]. However, clinically, depression is often accompanied by symptoms outside of the diagnostic criteria such as anxiety [2] and irritability [3,4].

Over the past 20 years, a preponderance of literature has suggested a subtype of MDD with anxious symptoms [5,6]. The presence of anxiety symptoms in depressed patients is associated with increased suicidality [2] more impaired functioning [7] worse quality of life [7] and overall severity in depression [2].

In 2013, the clinical significance of anxious features in depressed patients was acknowledged in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) with the addition of criteria for an anxious distress specifier for MDD [1]. The “with anxious distress” specifier is defined as the presence of at least two of the following five symptoms during most days of a major depressive episode: 1) feeling keyed up or tense, 2) feeling unusually restless, 3) difficulty concentrating because of worry, 4) fear that something awful may happen, and 5) feeling that the individual might lose control of himself or herself. In a 2014 study, patients meeting DSM-5 criteria for the anxious distress specifier reported poorer psychosocial functioning and quality of life than depressed patients who did not meet these criteria [8].

Irritability has also been commonly found in clinical cases of adults with MDD [3]. Although irritability is not a diagnostic symptom of

MDD among adults (as it can be in children and adolescents) nor considered a distinct subtype or specifier for MDD among adults, this symptom has been associated with greater overall severity in depression, anxiety comorbidity, disability, and suicidality among depressed patients [3,4,9].

Many studies have suggested that patients with MDD who exhibit symptoms of anxiety have a poorer response to pharmaceutical antidepressant treatment (ADT) compared with patients without comorbid anxiety [10]. However, data is lacking on how this finding relates specifically to patients who meet the MDD anxious distress specifier criteria, largely because of the newness of this specifier (introduced in DSM-5 in 2013). There is a paucity of data on irritability in unipolar depression and its relation to ADT response. However, in the STAR\*D observational study, irritability at baseline was associated with poorer study outcomes, including non-remission across subsequent therapeutic trials [11]. Additionally, little information exists relating to the overall relationships among symptoms of anxiety and irritability.

The objectives of this paper, comprising separate exploratory

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qualitative and quantitative evaluations, were focused on obtaining a better understanding of the relationships between anxiety and irritability and their association with depression and treatment response, as the overall goal of treatment for depression is the achievement of euthymia [12]. This paper presents the methods and results of the following two studies:

1. A qualitative study designed to understand anxiety better irritability, and other associated symptoms of depression in patients with MDD, as well as their impact from the patient perspective.

2. A quantitative evaluation of the relationship of anxious distress and irritability on outcomes for clinical study patients, with and without these symptoms at study baseline, who received ADT.

Although no a priori hypotheses were declared before the exploratory qualitative study related to the relationship among the associated symptoms (e.g., anxiety, irritability, aggression), specific findings were expected from the quantitative evaluation. Specifically, it was expected that clinical study patients with symptoms of anxious distress and/or irritability at baseline would demonstrate lower response rates to ADT than those without these symptoms.

## Methods

### Focus groups

Four group discussions, also known as focus groups, with patients with MDD were conducted in two different locations in the United States in April 2013. All patient focus groups were conducted by two PhD-level psychologists, both experienced in qualitative research in this therapeutic area, using a structured discussion guide. Inclusion criteria for focus group participants were as follows:

1. Age: 18 to 75 years
2. With a self-reported, clinician-confirmed diagnosis of MDD and at least 3 months in duration
3. Who self-reported "Often" experiencing anxiety, agitation, irritability, and/or aggression
4. Who were taking two or more medications to treat symptoms of depression (including an ADT)

The eight-item Center for Epidemiological Studies Depression Scale (CES-D-8) [13] was administered at the beginning of the focus groups to measure depressive symptoms. On a range of scores from 0 to 24, higher scores on the CES-D-8 denote more depressive symptoms and a score of 7 or higher suggests clinically significant levels of depressive symptoms [13]. Once participants completed the CES-D-8, they were asked open-ended questions designed to ascertain their specific definitions and experiences related to the target symptoms (anxiety, irritability, agitation, impulsivity, and aggression), how these symptoms were associated with depression, and what impact these symptoms had on their lives.

### Pooled clinical studies

#### Design

Select data were pooled from seven randomized, double-blind, placebo-controlled studies of adjunctive aripiprazole or brexpiprazole. The study designs and selection criteria have been described in previous publications [14-18]. Briefly, each study included an 8-week, open-label treatment phase with an ADT (phase A) followed by a randomized, double-blind treatment phase with the adjunct antipsychotic or placebo

(phase B). The study populations included patients aged 18 to 65 years with a diagnosis of MDD and experiencing a current depressive episode, a 17-item Hamilton Depression Rating Scale (HAM-D17) [19] a total Score  $\geq 18$  at screening and baseline visits, and a history of inadequate response to one to three ADTs for the current episode.

In the present analysis of the seven studies, an inadequate response throughout the 8 weeks of prospective ADT (phase A) was defined as having persistent symptoms without substantial improvement according to the following criteria:  $<50\%$  reduction in HAM-D17 from the start of the prospective phase, a  $<50\%$  reduction in Montgomery-Åsberg Depression Rating Scale (MADRS) [20] total score between the start of the prospective phase and each visit, and the Clinical Global Impression--Improvement (CGI-I) score  $\geq 3$  at each visit.

At the end of phase A, each study yielded a group of patients who were treatment responders and a group of patients with inadequate response to ADT (Table 1).

## Measures

### Depression

Each of the seven clinical studies used the following instruments to assess the severity of depressive symptoms: MADRS, HAM-D17, and Inventory of Depressive Symptomatology (Self-Reported) (IDS-SR) [21].

### Anxious distress

Proxy measurements were developed post hoc to ascertain the presence of the "with anxious distress" specifier at the phase A. Using a method similar to that used by Zimmerman and colleagues, a team of three clinicians reviewed the five DSM-5 anxious distress specifier criteria and the scale items of the three depression instruments (MADRS, HAM-D17, and IDS-SR) to match each specifier criterion to a relevant scale item. No proxy could be found for the criterion "Feeling that the individual might lose control of himself or herself"; thus, this criterion was excluded. Before analysis, clinicians discussed these pairings until consensus was reached for both the selected item for each specifier criterion and an appropriate item cut-off score based on the scale used for that item. Patients qualified as presenting with the "with anxious distress" specifier if they met two of the following four criteria:

1. Feeling keyed up or tense = MADRS item 3 (Inner Tension) score  $\geq 3$ , endorsing either "Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty" or "Unrelenting dread or anguish. Overwhelming panic"
2. Feeling unusually restless = IDS-SR item 24 (Feeling Restless) score  $\geq 2$ , endorsing either "I have impulses to move about and am quite restless" or "At times, I am unable to stay seated and need to pace around"
3. Difficulty concentrating because of worry = MADRS item 6 (Concentration Difficulties) score  $\geq 3$ , endorsing either "Difficulties concentrating and sustaining thought which reduced ability to read or hold a conversation" or "Unable to read or converse without great difficulty"
4. Fear that something awful may happen = HAM-D item 10 (Anxiety Psychic) score  $\geq 3$ , endorsing either "Apprehensive attitude apparent in face or speech" or "Fears expressed without questioning".

### Irritability

Similar to the definition of "substantial level of irritability" used in

Study Identifier	Study Phase	ADT Treatment (Phase A) Duration	Total N (Phase A)	Responder <sup>a</sup> n (%)	Citation or NCT#
33108211	2	8 weeks	663	341 (51.4)	00797966
33109222	2	8 weeks	622	312 (50.2)	01052077
33110227	3	8 weeks	1275	640 (50.2)	Thase et al., 2015 [15]
33110228	3	8 weeks	710	356 (50.1)	Thase et al., 2015 [14]
CN138139	3	8 weeks	619	332 (53.6)	Berman et al., 2007 [16]
CN138163	3	8 weeks	644	364 (56.5)	Marcus et al., 2008 [17]
CN138165	3	8 weeks	649	354 (54.5)	Berman et al., 2009 [18]
<b>Total</b>			<b>5,182</b>	<b>2,699 (52.1)</b>	

**Note:** ADT = Anti-Depressant Treatment; CGI-I = Clinical Global Impression--Improvement; HAM-D17 = 17-Item Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; NCT = National Clinical Trial.

<sup>a</sup>Participants who met criteria as a treatment responder at the end of the open-label ADT phase (week 8 of phase A) (i.e., a  $\geq 50\%$  reduction [improvement] on HAM-D17 from baseline to week 8;  $\geq 50\%$  reduction in MADRS total score between baseline and weeks 2, 4, 6, and 8; and a rating of 1 or 2 [very much or much improved] on the CGI-I at weeks 2, 4, 6, and 8).

**Table 1:** Clinical studies included in pooled analyses.

the STAR\*D study [3], the presence of irritability was defined by a score of  $\geq 2$  on the “Feeling Irritable” item of the IDS-SR (item 6). This item assesses irritability on a 0-to-3 scale, where a score of 2 represents “I feel irritable more than half the time” and a score of 3 represents “I feel extremely irritable nearly all of the time”.

## Analysis

### Qualitative assessment

Standard qualitative analytical methods were used to identify, characterize, and summarize patterns found in the focus group data.

### Quantitative assessment

The analyses for this study focused solely on patients in the phase A component of the seven studies—those receiving open-label ADTs. Data for each of the clinical studies were pooled for this analysis. Patients were divided into four groups based on the presence/absence of anxious distress and irritability at baseline: “anxious distress and irritability”; “anxious distress only”; “irritability only”; and “no anxious distress, no irritability.”

The proportions of treatment responders were compared across these four patient groups. Mean scores at baseline and week 8, as well as mean change from baseline to week 8, on items that define anxious distress and irritability for patients who were responders and those with inadequate response were also computed.

## Results

### Focus groups

**Participant characteristics:** The focus groups included a total of 30 participants with a mean age of 47.3 (standard deviation (SD) = 13.3) years; 66.7% were female; and 80.0% were white. Participants were diagnosed with MDD a mean of 14.7 (SD = 10.7) years prior (range, 1-41 years).

Among the associated symptoms reported at screening, anxiety was reported by 87% (n = 26) of the participants; irritability, 80% (n = 24); agitation, 60% (n = 18); and aggression, 10% (n = 3). All participants in the qualitative study were required to have at least one of the four associated symptoms/behaviors to participate. The mean CES-D-8 score across all focus group participants was 10.3 (SD = 5.1), with 23 participants (76.7%) scoring a 7 or greater, which indicates clinically significant levels of depressive symptoms.<sup>13</sup>

### Symptom experiences

During the focus group, participants generated an exhaustive list

of symptoms and behaviors associated with depression and provided additional detail pertaining to the target symptoms of interest.

**Anxiety:** All participants understood anxiety and could easily describe it from their own perspective. All participants reported experiencing anxiety or having various forms of anxious feelings that they associated with their depression. Words and phrases used to describe anxiety included feeling “like you will jump out of your skin,” “jittery and fidgety,” “apprehension,” and feeling “out of control.”

Participants described anxiety as including both physical and mental components and often involving worry or fear, as well as a racing heart and/or feelings of nervousness. Descriptions included “I feel like my heart’s racing. My palms are sweating. I’m all tingly,” “I’m constantly waiting for the next health issue to hit,” and “Mentally if I get anxious, and of course physically, because I’ll tighten and tense up my muscles, and then the stress builds.”

**Irritability:** All participants understood the target symptom of irritability and could easily define it in their own words, albeit using a variety of terms and synonyms. Participants referred to irritability as a feeling of general frustration, annoyance, and bother, often resulting in a short temper or less patience when interacting or communicating with others. Specifically, “You can’t tolerate anything. I can’t tolerate anything,” “You’re not at peace. You’re just not okay with the way things are. It’s like a simmering pot,” and “I’m in such a state that everything’s bugging me.”

**Agitation:** Most participants said that agitation was similar to irritability; however, agitation was not a word that was easily defined or quickly associated with depression. Overall, although agitation was recognized as a symptom most participants experienced, the term was not commonly used. A few participants described agitation similar to irritability but with a slightly more physical component (i.e., restlessness, nervousness).

**Aggression:** Although only a minority of participants reported experiencing aggression in the past, and even fewer at the time of the focus groups, participants were able to discuss and expound upon the meaning of aggression. The definition of aggression was generally agreed to be an act of physical or verbal violence or acting out or an expression of internalized anger and rage like one is “on the attack” and is “initiating an argument or altercation”. One patient explained that “anxiety, worry, fear, anger, irritability, and frustration are things that we feel inside; aggression is how you choose to act”.

### Relationship among and impact of associated symptoms

Once the focus group participants described and defined the target

symptoms, discussion focused on the relationship among them as well as their impact.

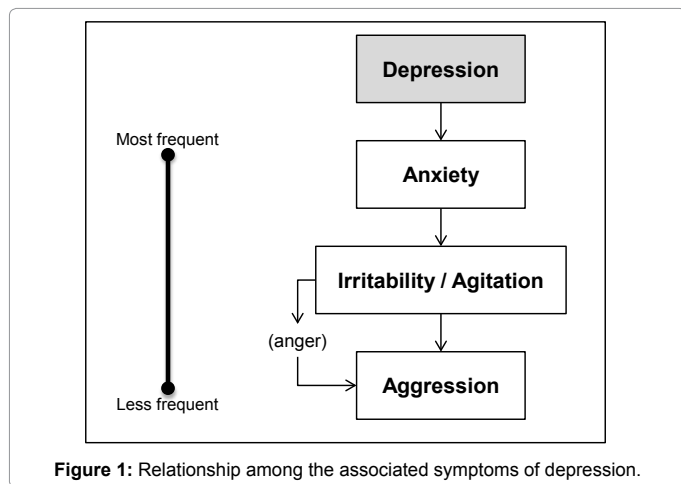
Anxiety was considered to occur most frequently among the four target symptoms and was often believed to be the beginning or source of the others, directly leading to irritability, agitation, and sometimes aggression. Irritability and agitation were generally perceived as synonymous, although a few participants believed that agitation was a more extreme or physical version of irritability or anxiety. Aggression was usually an endpoint or extreme emotion and behavior resulting from the other symptoms (Figure 1).

Most participants reported anxiety as the target symptom with the greatest level of impact on their lives-both in terms of the breadth and the depth of each impact area. The impact of anxiety was noted across all areas of participants' lives: family, work, social, sleep, and financial.

### Treatment

Many participants noted a general lack of efficacy of their antidepressant medications in treating their anxiety. Although some participants stated that their antianxiety treatments did help reduce their anxiety, they still frequently experienced anxiety. A few participants said that taking antianxiety medications came with a price, specifically by either increasing depressive symptoms or having incapacitating levels of sedation. For instance, one patient stated that "it relieves the anxiousness and the anxiety and the fear. It does calm that down, but I feel like I end up more physically and emotionally depressed".

Of the four target symptoms/behaviors discussed, participants



noted that anxiety was the symptom they would most like a medication to treat, as they believed anxiety to be the source or underlying cause of the other target symptoms.

### Pooled Clinical Studies

A total of 5,182 patients participated in phase A across the clinical studies. At baseline, 75.2% of patients met criteria for MDD with anxious distress and 62.2% for MDD with irritability. Anxious distress and irritability coexisted frequently, with 52.0% of patients presenting with both at baseline; 23.2% of patients presented with anxious distress only, 10.2% with irritability only, and 14.6% of patients did not meet criteria for either anxious distress or irritability (Table 2).

Among the 5,182 patients, 52.1% (n = 2,699) were considered treatment responders to ADT. Compared with the response rate for patients with neither anxious distress nor irritability (n = 431, 56.9%), response rates for patients with anxious distress and irritability (n = 1,366, 50.7%, P = .027) and for those with anxious distress only (n = 607, 50.5%, P = .046) were significantly lower. No difference was observed in the response rates between patients with neither anxious distress nor irritability (n = 431, 56.9%) and those with irritability only (n = 295, 56.1%).

Compared with baseline scores for ADT responders, the anxiety and irritability items were numerically higher (more severe) in patients with subsequent inadequate response (Table 3). On all items, mean change scores at week 8 also were numerically lower in patients with inadequate response, denoting less improvement.

### Discussion

Based on the feedback from the patient focus groups, anxiety and irritability were frequently reported and were often comorbid with depressive symptoms. According to patients' reports, the relationship between these two symptoms appears strong, as anxiety is often the beginning or source of irritation (as well as agitation and aggression). Anxiety, irritability, and even agitation (although not a term frequently used by patients) were defined with many of the words and concepts that comprise the definition and criteria for anxious distress (e.g., nervous, tense, restless, worry, fear). Similarities to the description feeling "out of control" (one of the five criteria for anxious distress) also could be found in the way some patients described anxiety and aggression (e.g., "jump out of your skin," acting out).

Many patients in the focus groups expressed an unfulfilled need to relieve their anxiety associated with depression and believed that improvements in their anxiety would also reduce their other associated symptoms such as irritability and agitation. As the impact of anxiety on

Study Identifier	Anxious Distress & Irritability		Anxious Distress Only		Irritability Only		No Anxious Distress, No Irritability	
	n	Responders, n (%)	n	Responders, n (%)	n	Responders, n (%)	n	Responders, n (%)
33108211	381	183 (48.0)	134	67 (50.0)	57	34 (59.6)	91	57 (62.6)
33109222	337	161 (47.8)	157	87 (55.4)	64	37 (57.8)	64	27 (42.2)
33110227	592	282 (47.6)	313	155 (49.5)	142	75 (52.8)	228	128 (56.1)
33110228	351	179 (51.0)	180	83 (46.1)	60	31 (51.7)	119	63 (52.9)
CN138139	319	171 (53.6)	138	73 (52.9)	68	34 (50.0)	94	54 (57.4)
CN138163	351	193 (55.0)	122	65 (53.3)	77	45 (58.4)	94	61 (64.9)
CN138165	365	197 (54.0)	158	77 (48.7)	58	39 (67.2)	68	41 (60.3)
<b>Total</b>	<b>2,696 (52.0)<sup>a</sup></b>	<b>1,366 (50.7)<sup>b</sup></b>	<b>1,202 (23.2)<sup>a</sup></b>	<b>607 (50.5)<sup>b</sup></b>	<b>526 (10.2%)<sup>a</sup></b>	<b>295 (56.1)</b>	<b>758 (14.6)<sup>a</sup></b>	<b>431 (56.9)</b>

Note: ADT = Anti-Depressant Treatment.

<sup>a</sup> Based on the total sample across the 7 clinical studies, N = 5,182.

<sup>b</sup> Statistically significantly lower than the "No anxious distress, No irritability" subgroup at P < 0.05.

**Table 2:** Response rates to ADT by anxious distress and irritability subgroups.



Concept/Item	Baseline Mean (SD)	Week-8 Mean (SD)	Change Mean (SD)
<b>Anxious Distress</b>			
<b>Feeling keyed up or tense</b>			
Responders	3.02 (0.94)	1.28 (1.12)	-1.75 (1.33)
Inadequate response	3.13 (0.96)	2.70 (1.09)	-0.42 (1.07)
<b>Feeling unusually restless</b>			
Responders	0.99 (0.87)	0.45 (0.66)	-0.54 (0.92)
Inadequate response	1.06 (0.92)	0.9 (0.84)	-0.15 (0.86)
<b>Difficulty concentrating because of worry</b>			
Responders	3.29 (1.09)	1.30 (1.28)	-2.00 (1.50)
Inadequate response	3.45 (0.96)	3.03 (1.08)	-0.42 (1.08)
<b>Fear that something awful may happen</b>			
Responders	2.09 (0.69)	0.83 (0.77)	-1.26 (0.94)
Inadequate response	2.13 (0.69)	1.83 (0.75)	-0.30 (0.78)
<b>Irritability</b>			
Responders	1.66 (0.79)	0.55 (0.63)	-1.11 (0.86)
Inadequate response	1.70 (0.80)	1.22 (0.80)	-0.48 (0.83)

Note: SD = Standard Deviation.

Table 3: Anxious distress and irritability item scores at baseline and week 8.

daily lives was reportedly the greatest among the associated symptoms, this study suggests that further relief of anxiety would result in less burden overall for individuals with MDD.

The relationship between anxiety and irritability was further explored using data from pooled clinical studies. Consistent with previous research, we found that many patients with an inadequate response to ADTs presented with symptoms of anxious distress and irritability at baseline. Specifically, approximately 75% of patients presented with symptoms of anxious distress as defined using proxies for the DSM-5 specifier, and approximately 60% of patients presented with irritability. Anxiety (anxious distress) was more prevalent than irritability and also tended to encompass irritability. More patients with irritability had anxious distress ( $n = 2,722$ , 84.4%) compared with the number of patients with anxious distress who also had irritability ( $n = 2,722$ , 69.8%). However, symptoms of anxious distress greatly overlapped with irritability. Approximately two-thirds of patients with anxious distress also presented symptoms of irritability. On the contrary, irritability alone was present in only 10% of patients.

Our hypothesis regarding ADT response rates was partially met because the presence of anxious distress was associated with a decreased likelihood of response to another ADT, but in the absence of anxious distress, response rates did not significantly differ (e.g., between patients with irritability only and those with neither anxious distress nor irritability).

Limitations of the qualitative study involve weaknesses typical for this methodology such as the small sample size, lack of sample representativeness, and inability to generalize results. A limitation of the quantitative evaluation is the method of measurement used for the constructs of anxious distress and irritability. Although the method of measurement was similar to that used in a previous study [3,8], both approaches involved post hoc measurements and both measurements were without previous use or validation. Additionally, in terms of the five criteria for the DSM-5 specifier of anxious distress, only four items were identified, one for each of four criteria, excluding one for the fifth criterion, “lose control of himself or herself.” Also, using single items for each of the anxious distress concepts and for irritability potentially questions the stability and reliability of the measurements. Future studies evaluating the anxious distress concept should use validated measures with multiple items per concept for greater

confidence in findings. Regardless, findings from both the qualitative and quantitative results of this paper suggest that there is indeed an important association among anxiety, irritability, and depression and one that potentially affects response to ADT.

## Conclusion

Results from these two independent samples confirmed that various anxiety symptoms, including those comprising anxious distress as defined in DSM-5, are prevalent and meaningful in depression and frequently associated with irritability. In patients with an existing inadequate response to ADTs, symptoms of anxious distress are associated with a decreased likelihood of response to another ADT. Further research in evaluating the impact of treating anxiety and irritability symptoms along with MDD is warranted.

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## Transparency

### Declaration of funding

This study was funded by Lundbeck SAS. Lundbeck SAS provided funding to RTI Health Solutions to design and implement the study and to develop the manuscript. Lundbeck collaborated with RTI Health Solutions in study design, interpretation of data, the decision to submit the manuscript for publication, and approval of the final manuscript.

1. ND is an employee of Lundbeck SAS, sponsor of the study; she collaborated on study design, interpretation of study results, and development of the manuscript.
2. EW is an employee of Lundbeck SAS, sponsor of the study; she collaborated on interpretation of clinical study results and development of the manuscript.
3. DBD and TMB are employees of RTI Health Solutions, contracted by Lundbeck SAS to design and implement this study. DBD designed and cofacilitated the interviews and focus groups, collaborated on the analysis and interpretation of study results, and contributed to development of the manuscript. TMB collaborated on the design of the study, cofacilitated the interviews and focus groups, analyzed the qualitative data, interpreted both qualitative and quantitative study results, and contributed to development of the manuscript. Neither DBD nor TMB were involved in the analysis of the original clinical study results—only the interpretation of results as related to those included in this paper.
4. MF (Fava) developed the anxious distress and irritability concept algorithms, collaborated on the design of this paper, and contributed to development of the manuscript.

### Declaration of financial/other relationships

All authors contributed equally to the work. ND and EW are employed by Lundbeck SAS, sponsor of this study. TMB and DBD are employed by RTI Health Solutions, the organization conducting the work. MF is a paid medical consultant for Lundbeck SAS. The authors have no additional financial relationships or otherwise to declare.

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