Patients with anxious depression: overview of prevalence, pathophysiology and impact on course and treatment outcome

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Abstract

**Purpose of review:** Major Depressive Disorder (MDD) with a comorbid anxiety disorder or with significant anxiety symptoms (here called anxious depression) is common and has been associated with poor clinical course trajectories. However, various dichotomous as well as dimensional definitions have been used to label anxious depression and it remains unclear to which extent these result in inconsistent findings. This review provides an overview of recent literature on the impact of anxiety in depressed patients on clinical course trajectories, treatment outcomes, and underlying neurobiological dysregulations.

**Recent findings:** Anxious depression seems associated with poorer clinical course trajectories and treatment non-response as compared to ‘pure’ depression, regardless of which definition is used. Recent studies have attempted to determine specific efficacy of novel pharmacological treatments for anxious depressed patients, but have not been conclusive because of the insufficient number of studies and differences in definitions and assessment of anxious depression. Neurobiology studies suggest that anxious depression is associated with increased immune dysregulation, more cortical thinning and corticolimbic dysfunctions as compared to ‘pure’ depression.

**Summary:** Anxious depression appears to be a common and clinically relevant subtype of depression as it predicts poorer course trajectories. As populations with anxious depression may benefit from specific treatment regimens, further research is necessary to better delineate its definition and neurobiology. The relatively new DSM-5 anxious distress specifier is a welcome development and should be further investigated and compared against other anxiety constructs.

**Keywords:** Depressive disorder; anxious distress; anxiety disorder; comorbidity; treatment; neurobiology
Introduction

The co-occurrence of anxiety in depression is common [1] and has been extensively studied, but various concepts and definitions have been used for this co-occurrence [2,3]. Generally, the term ‘anxious depression’ has been used interchangeably in recent literature to denote three common dichotomous anxiety-depression definitions: 1) Major Depressive Disorder (MDD) with a comorbid full-blown anxiety disorder, 2) MDD with anxiety symptoms measured as an above cut-off score on an anxiety severity scale [2], and 3) MDD with the DSM-5 anxious distress specifier (i.e. at least 2 out of 5 general anxiety symptoms). Although prior studies have often focused on dichotomous classifiers for anxious depression, others have expressed the concept as a continuous dimension. Consequently, various definitions for anxious depression are being used across studies, making results not always directly comparable.

Why is anxious depression worth clinical and research attention, and does its exact assessment play an important role in this? The clinical relevance becomes clear from recent studies illustrating that patients with anxious depression, as compared to ‘pure’ depression patients, generally may have greater depression chronicity and severity [1,4-7], higher suicide risks [8-10], less treatment response [11-16] and a differential neurobiological profile [17]. This review provides a timely overview of recent literature on the impact of anxious depression on clinical course trajectories and outcomes, treatment outcomes, and touches upon possible underlying neurobiological dysregulations. In doing so, it will—wherever possible—pay attention to whether findings are depending on the various definitions and methods used to classify anxious depression. Although co-occurring anxiety is also highly common in bipolar depression and is associated with poor clinical outcomes [1], it is beyond the scope of the review. Likewise, DSM-IV mixed anxious-depressive disorder (MADD) is also not included in this review, as it was omitted in DSM-5 after showing insufficient reliability in DSM-5-field trials [18-20].
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Diagnostic assessment of anxious depression

Ionescu et al. (2013) in their review proposed a syndromal and a dimensional definition of anxious depression [2]. Accordingly, a **syndromal** definition includes presence of a *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-based or *International Classification of Diseases* (ICD)-based depressive disorder diagnosis and one or more comorbid anxiety disorder diagnoses. Variation in the number, type, and timeframe of depressive and comorbid anxiety disorders introduces heterogeneity in the syndromal definition of anxious depression. A **dimensional** definition requires diagnosis of a DSM- or ICD-based depressive disorder plus significant anxiety symptoms assessed on a dimensional rating scale [2]. The Hamilton Depression Rating Scale (HAM-D) anxiety/somatization factor (ASF) score with a cut-off ≥7 and the Hamilton Anxiety Rating Scale (HAM-A) with varying cut-off scores are among the most frequently used diagnostic criteria in dimensional definitions of anxious depression [2]. However, various scales and different cut-off points to determine relevant anxiety symptoms have been used, resulting in heterogeneity in the dimensional definition as well [2,3]. While it has been suggested that a dimensional definition of anxious depression is clinically most relevant [2,3,21*], up until now, no uniform definition has been established.

New developments in the field of anxious depression may contribute to a more uniform, clinically relevant definition. The DSM-5 includes a new **anxious distress specifier** to acknowledge the clinical significance of prominent anxiety features in MDD [22]. The DSM-5 criterion for the anxious distress specifier is endorsement of at least two of the following five symptoms during the majority of a major depressive episode: feeling keyed up or tense, feeling unusually restless, difficulty concentrating because of worry, fear that something awful might happen, and feeling of losing control [22]. Of these, four out of five symptoms are typical for Generalized Anxiety Disorder (GAD) and one for Panic Disorder (PD) [23]. However, a recent study examining the validity of the specifier suggests that the specifier is a generic anxiety marker, as it did not show specificity with GAD and PD [24*]. The specifier was derived from the study by Goldberg and others [25], who produced a brief 5-item anxiety scale by item-response analyses to facilitate the diagnostic assessment of anxious depression [25]. In a recent field study conducted across four countries, this short anxiety scale was compared with the revised Clinical Interview Schedule (CIS-R), and found to be clinically useful as it was able to identify current anxiety in the majority of individuals [26]. Furthermore, recent findings demonstrated that the anxious distress specifier is a reliable and clinically valid construct [24*,27,28*], and that a measure of the DSM-5 anxious distress specifier, the DSM-5 anxious distress specifier interview, had comparable validity as the HAM-A in measuring anxiety in depression [28*]. Therefore, short screening and diagnostic scales developed for anxiety assessment such as the anxious distress specifier may be
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Clinically useful, as they are more feasible and easy to incorporate in clinical practice, as opposed to formal diagnostic assessment of anxiety disorders which requires thorough, time-consuming interviews.

**Prevalence of anxious depression**

Recently, several large studies showed high comorbidity rates of anxiety disorders in depression, regardless of the used definition [29-32]. For instance, a study among 74,045 adults in 24 countries showed a high cross-national consistency of anxiety-depression comorbidity [30]. Of persons with lifetime MDD, 46% had at least one lifetime anxiety disorder, and of those with a 12-month MDD, 52% had lifetime anxiety disorders and 42% had 12-month anxiety disorders [30]. Additionally, a prevalence rate of 72% of comorbid GAD in 667 psychiatric outpatients with MDD was observed [32]. In terms of temporal order, of those with lifetime comorbid anxiety disorder and MDD, 68% reported an earlier occurrence of their first anxiety disorder versus their MDD, whereas in 13.5% anxiety followed after MDD onset and in 18.5% the occurrence of the anxiety disorder was parallel to that of depression [30]. Recent as well as other previous studies [4,33-35] also showed that generally the onset of anxiety disorders precedes the onset of depression, suggesting that a temporal priority of anxiety disorders may contribute to the development of depression [36,37].

A high prevalence of anxious depression has also been reported in studies using dimensional definitions of anxious depression. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study showed that 53% of 2,876 MDD patients had anxious depression (MDD plus a HAM-D ASF score ≥7) [12], and a Chinese population study using the same definition, found that 70% of 375 MDD patients had anxious depression [13]. Recent studies using the anxious distress specifier definition reported prevalence rates of anxious distress ranging from 54–78% in patients with MDD [10,24*,27,38-40]. These findings demonstrate that prevalence rates of anxious depression are high, independent of the used definition. It is important to note that different definitions do not necessarily capture the same patients though; the DSM-5 anxious distress specifier for example poorly overlapped with comorbid DSM-IV-based anxiety disorders (Cohen’s κ=0.09) [24*].

**Impact of anxious depression on clinical course trajectories and outcomes**

Substantial evidence suggests that MDD with comorbid anxiety disorders is associated with chronic course trajectories [7,35] and poor clinical outcomes [4,29,31*,32,41,42] in clinical samples. Recently, multiple large-scale studies have reported that patients with depression and comorbid anxiety disorders had higher readmission rates [35], lower remission rates [41], greater depression severity [31*,41], higher suicidal risks [29,31*], a lower quality of life (QOL) [32,41], impaired social and occupational dysfunction [29], and an
increased comorbidity of somatic conditions such as asthma, diabetes and hypertension [31*]. Some of these studies found distinct outcomes dependent on the type and number of comorbid anxiety disorders [29,31*]. For instance, Dold and colleagues [31*] demonstrated a higher depression severity in patients with MDD and comorbid GAD or social anxiety disorder (SAD), but not in those with comorbid PD or Agoraphobia; whereas higher suicide risk was specific to MDD patients with comorbid PD, Agoraphobia and SAD. Another study observed a higher suicide risk and greater dysfunction in patients with MDD and ≥2 anxiety disorders compared to those with a comorbid SAD [29]. Research shows that MDD with high anxiety symptom levels is also clinically relevant [1]. Either measured with the HAM-D ASF score or HAM-A, depressed patients with anxiety symptoms generally have greater depression chronicity and severity [1,5,6], higher suicide ideation and risks [1,8,9], and lower QOL than MDD patients without anxiety. Also, anxious depression defined with the anxious distress specifier was associated with greater depression severity, higher suicidal ideation, decreased QOL, greater self-reported impairment, severe insomnia [10,40], and increased incidence of cardiovascular disease [43]. Overall, anxious depression seems to be associated with poorer course trajectories and worse clinical outcomes. When comparing various comorbid anxiety definitions, one recent study showed that the DSM-5 anxious distress specifier outperformed the comorbidity indicator of DSM-IV-based anxiety disorders in predicting subsequent chronicity, a longer time to remission, and greater functional disability in depressed patients [24*]. This suggests that the anxious distress specifier may identify a clinically relevant subgroup of MDD patients predictive of poor clinical outcomes, which may not be fully captured in DSM-based anxiety disorder diagnoses.

**Impact of anxious depression on treatment outcomes**

In the past, it has been found in several [11-16], but not all [44-49] studies that depressed persons with concurrent anxiety symptoms had poorer treatment response than those with ‘pure’ depression. A previous, large review [14] showed that patients with dimensionally defined anxious depression did respond to traditional antidepressants, but that they were unable to maintain response or remission and suffered from greater frequency of side effects than patients with non-anxious depression [14]. When this review [14] was conducted in 2014, studies on the DSM-5 anxious distress specifier were not yet available. Recently, one study showed that within MDD patients, the presence of (DSM-5 based) anxious distress predicted subsequent poor treatment outcomes and a greater frequency of antidepressant side effects in depressed patients who received adequate antidepressant treatment, whereas presence of comorbid DSM-IV-based anxiety disorders did not [38]. Mixed findings were observed for specific comorbid anxiety disorders with respect to treatment response. For instance, a recent naturalistic study across eight European countries conducted among 1,346 patients with MDD showed that those with a comorbid GAD...
showed poorer treatment response to antidepressant medication compared to comorbid PD [31]. Another recent study reported a higher likelihood to experience antidepressant side effects only in MDD cases with comorbid PD versus those without, but not in those with comorbid SAD or GAD [50]. Benzodiazepines are recommended as ‘bridging strategy’ as they are effective in achieving rapid control of initial anxiety in depressed patients with a comorbid anxiety disorder, but are disapproved in those with substance abuse due to a high risk of dependence [51]. Atypical antipsychotics are recommended instead [51], but only quetiapine seems effective in depressed patients with a comorbid GAD. Some of the atypical agents may have an unfavorable side effect profile [52], limiting its use in depressed patients with comorbid anxiety as they may suffer from greater side effects [14]. Overall, these findings emphasize the need to investigate novel pharmacological treatments that may be specifically effective in patients with anxious depression, in addition to conventional therapies.

While previous treatment studies have mainly focused on traditional antidepressants, new research has emerged investigating novel treatment options in patients with anxious depression (Table 1). Efficacy of atypical antipsychotics has been sparsely investigated. One large study found efficacy of quetiapine adjunct therapy in both patients with anxious and non-anxious depression [53]. However, the findings were inconsistent across definitions of anxious depression and different quetiapine dosages [53]. Another study also found efficacy for quetiapine therapy in patients with anxious depression, but did not directly compare this with a non-anxious depressed patient group and the sample size was very small (n=9) [54]. In both MDD patients with and without anxious distress, adjunctive brexpiprazole was effective [55*]. Two studies examining the efficacy of ziprasidone showed that this was not effective in patients neither with nor without anxious depression [56,57].

Patients with anxious depression however responded better to a single infusion of ketamine than those with non-anxious depression [58]. Also, vilazodone—a serotonin reuptake inhibitor and 5-hydroxytryptamine 1A (5-HT1A) receptor partial agonist—was more effective in 708 patients with anxious depression than in 155 patients with non-anxious depression, although the sample size of those with non-anxious depression was very small [59]. While several other recent studies have investigated efficacy of novel pharmacological treatments for anxious depression, they did not compare efficacy with non-anxious depression [60-63] (Table 1).
### Table 1. Pharmacological studies examining treatment response specifically in patients with anxious depression

<table>
<thead>
<tr>
<th>Research design</th>
<th>Intervention treatment</th>
<th>Control treatment</th>
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<td><strong>Atypical antipsychotics</strong></td>
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<tr>
<td>Bandelow et al. 2014 [53]</td>
<td>Post-hoc analyses of pooled data from two 6-week, double-blind, randomized studies</td>
<td>Quetiapine-XR adjunct therapy</td>
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<td>Li et al. 2016 [54]</td>
<td>Randomized, double-blind, 8-week, comparison pilot study</td>
<td>Quetiapine-XR mono- or adjunctive therapy</td>
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<td>McIntyre et al. 2016 [55*]</td>
<td>Post-hoc analysis utilizing data from two similarly designed randomized, double-blind, phase III studies comprising a screening phase (7–28 days), an 8-week single-blind prospective phase, and a double-blind, 6-week, randomized treatment phase.</td>
<td>Brexpiprazole adjunct therapy</td>
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<tr>
<td>Ionescu et al. 2016 [56]</td>
<td>Randomized, double-blind, parallel-group, 8-week trial</td>
<td>Ziprasidone augmentation of escitalopram</td>
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<td>Heo et al. 2015 [57]</td>
<td>Post-hoc analysis utilizing data from a multi-center, randomized, double-blind trial</td>
<td>Ziprasidone monotherapy (oral)</td>
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<td><strong>Serotonin reuptake inhibitor and 5-HT1A receptor partial agonist</strong></td>
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<td>Thase et al 2014 [59]</td>
<td>Post-hoc analysis of two phase III, randomized, double-blind, multi-center 8-week studies</td>
<td>Vilazodone monotherapy</td>
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<td>Efficacy assessment</td>
<td>Participants</td>
<td>Anxious depression definition</td>
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<td>MADRS total score</td>
<td>N=919 patients with anxious and non-anxious MDD and an inadequate response to antidepressants</td>
<td>Primary analysis: DSM-IV MDD plus HAM-A total score ≥20 at baseline (n=433)</td>
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<td>Secondary analysis: DSM-IV MDD plus HAM-D&lt;sub&gt;0&lt;/sub&gt; ASF score ≥7 at baseline (n=697, 75.8%)</td>
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<td>HAM-D&lt;sub&gt;0&lt;/sub&gt;, HAM-A, CGI-S, QIDS-SR total scores</td>
<td>N=9 patients with MDD and comorbid current GAD (who completed the study)</td>
<td>DSM-IV MDD with HAM-D&lt;sub&gt;0&lt;/sub&gt; ≥18 at screening and baseline, and a current GAD with HAM-A ≥18 at screening and baseline</td>
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<td>MADRS total score</td>
<td>N=989 patients with MDD with and without anxious distress</td>
<td>DSM-IV-TR MDD plus meeting criteria of 2 out of 4 proxy items for the DSM-5 anxious distress specifier (n=550, 55.6%)</td>
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<td>HAM-D&lt;sub&gt;0&lt;/sub&gt; and HAM-A total scores</td>
<td>N=139 patients with anxious and non-anxious MDD</td>
<td>DSM-IV MDD plus HAM-D&lt;sub&gt;0&lt;/sub&gt; ASF score ≥7 at baseline (n=38, 27.3%)</td>
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<td>HAM-D&lt;sub&gt;0&lt;/sub&gt; and QIDS-SR total score</td>
<td>N=120 patients with anxious and non-anxious MDD</td>
<td>DSM-IV MDD, HAM-D&lt;sub&gt;0&lt;/sub&gt; ≥14, and QIDS-SR ≥10 plus HAM-D&lt;sub&gt;0&lt;/sub&gt; ASF score ≥7 at baseline (n=60, 50.0%)</td>
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<td>Depressive symptoms: HAM-D&lt;sub&gt;0&lt;/sub&gt; and MADRS total scores</td>
<td>N=863 patients with anxious and non-anxious depression</td>
<td>DSM-IV-TR MDD plus HAM-D ASF score ≥7 at baseline (n=708, 82.0%)</td>
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### Table 1. Continued

<table>
<thead>
<tr>
<th>Glutamatergic medications</th>
<th>Research design</th>
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<tr>
<td>Ionescu et al. 2014 [58]</td>
<td>Post-hoc study with a 28 days follow-up duration</td>
<td>Single infusion of ketamine (Glutamatergic NMDA receptor antagonist)</td>
<td>No control group</td>
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<td>Kent et al. 2016 [60]</td>
<td>Phase 2, double-blind, flexibly-dosed, multi-center study consisting of a 2-week screening phase, 8-week double-blind treatment phase (doubly randomized design including 2 periods of 4 weeks each), and 2-week posttreatment follow-up phase</td>
<td>Metabotropic glutamate 2 receptor positive allosteric modulator JNJ-4041813/ ADX71149</td>
<td>Placebo</td>
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<td>Selective delta opioid receptor</td>
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<td>Richards et al. 2016 [61]</td>
<td>Single center, double-blind, randomized, parallel group design, phase II pilot study</td>
<td>Selective delta opioid receptor AZD2327</td>
<td>Placebo</td>
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<td>SSRI</td>
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<td>Jiang et al. 2017 [62]</td>
<td>24-week, open-label, single-arm, prospective study</td>
<td>Escitalopram</td>
<td>No control group</td>
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<td>Other</td>
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<td>Ghajar et al. 2017 [63]</td>
<td>Double-blind, controlled trial</td>
<td>Crocus Sativus L</td>
<td>Citalopram</td>
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Abbreviations: MDD, Major Depressive Disorder; XR, Extended release; MADRS, Montgomery–Åsberg Depression Rating Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders; TR, Text Revision; GAD, Generalized Anxiety Disorder; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; ASF, anxiety/somatization factor; CGI-S, Clinical Global Impression-severity; CGI-I, Clinical Global Impression-improvement;
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<tr>
<th>Efficacy assessment</th>
<th>Participants</th>
<th>Anxious depression definition</th>
<th>Efficacy Intervention-Control treatment</th>
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<td>Intervention treatment dosage</td>
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<td>Anxious MDD</td>
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<td>Non-anxious MDD</td>
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<td>MADRS total score</td>
<td>N=26 inpatients with treatment-resistant anxious and non-anxious MDD</td>
<td>DSM-IV MDD plus HAM-D₀ ASF score ≥7 at baseline (n=15, 57.7%)</td>
<td>0.5mg/kg over 40min</td>
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<td>HAM-A₀ total score</td>
<td>N=100 patients with anxious depression (who completed both treatment periods) and an insufficient response to current SSRI/SNRI treatment</td>
<td>DSM-IV MDD, HAM-D₀ total score of ≥18 and HAM-D₀ ASF score ≥7 (N=100)</td>
<td>50–150mg/twice daily</td>
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<td>HAM-D₀ and HAM-A total scores</td>
<td>N=22 patients with anxious depression</td>
<td>DSM-IV MDD, HAM-D total score ≥20, HAM-A total score ≥16, and CGI-S score ≥4 at screening and randomization plus HAM-D ASF score ≥7 (N=22)</td>
<td>3mg/kg/day</td>
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<td>MADRS, HAM-D₀ and HAM-A, CGI-S, and CGI-I total scores</td>
<td>N=191 patients with anxious depression (in full-analysis set who completed the study)</td>
<td>DSM-IV-TR MDD, MADRS total score ≥22 and HAM-A total score ≥14 (N=191)</td>
<td>10–20 mg/day</td>
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<tr>
<td>HAM-D and HAM-A total scores</td>
<td>N=60 patients with MDD and anxious distress (who completed the study)</td>
<td>MDD plus anxious distress</td>
<td>30mg/day</td>
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Abbreviations: MDD, Major Depressive Disorder; XR, Extended release; MADRS, Montgomery–Åsberg Depression Rating Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders; TR, Text Revision; GAD, Generalized Anxiety Disorder; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; ASF, anxiety/somatization factor; CGI-S, Clinical Global Impression-severity; CGI-I, Clinical Global Impression-improvement; QIDS-SR, Quick Inventory of Depressive Symptomatology Self-Rated; NMDA, N-methyl-D-aspartate; JNJ, Johnson and Johnson; AZD2327, 4-[(N,N-diethylbenzamide; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor. Symbol: - Intervention treatment is not effective (statistically non-significant), + Intervention treatment is effective (statistically significant), N/A= Not applicable since there is no control group of patients with non-anxious depression.
In summary, recent studies have attempted to investigate the effectiveness of several novel pharmacological treatments, either as monotherapy or as adjunctive therapy, for patients with anxious depression. However, these studies are very scarce and have some important limitations: not all studies directly compared efficacy for anxious depression with a non-anxious depressed group, many studies used post-hoc analyses and therefore had limited sample sizes. Thus, current evidence is insufficient to establish whether novel pharmacological treatments are specifically beneficial for patients with anxious depression. Clearly, further research to address this question is needed.

**Underlying neurobiological pathophysiology of anxious depression**

Several neurobiological mechanisms have recently been implicated in the pathophysiology of MDD, such as alterations in regional brain volumes and disturbances in the main neurobiological stress-responsive systems including the hypothalamic-pituitary-adrenal (HPA)-axis and the immune system [64]. Anxious depression may have a distinct neurobiology that separates it from non-anxious depression. A better understanding of the neurobiological profile of anxious depression may aid not only its definition, but also its recognition as a distinct subtype of MDD and ultimately its treatment [17]. This section will touch upon some of these recent findings in pathophysiology.

To date, few studies have examined the link between inflammation and anxious depression. In patients with MDD and moderate-severe to severe anxious distress, higher monocyte counts have been found compared with mild to moderate anxious distress [65]. Also, decreased venous blood basophil counts and increased fragmented neutrophils were observed in patients with MDD and higher levels of anxiety [66]. These alterations in white blood cell subset counts indirectly point to alterations in the immune system, suggesting a role of inflammation in the pathophysiology of anxious depression. Moreover, higher innate cytokine production capacity, rather than higher basal inflammation, was associated with anxious distress as well as with other dimensional anxiety indicators in a large MDD sample [67*]. Anxious depression has also been related to HPA-axis dysregulations: patients with anxious depression had a significantly attenuated adrenocorticotropic hormone response than patients with non-anxious depression and controls after intravenous corticotropin-releasing hormone challenge test, though samples were small [17,68]. Two recent small studies showed however that dimensional anxiety measures were not associated with hair cortisol levels in female MDD samples [69,70], whereas comorbid anxiety moderated stress-induced cortisol levels in MDD in a sex-dependent manner [71].
In terms of brain structure, high levels of anxiety and comorbid anxiety in depression relative to non-anxious depression have been associated with cortical thinning in the orbitofrontal and anterior cingulate cortex (ACC), insula, and temporal lobes [72-74], regions strongly connected to the limbic system. Cortical thinning in these regions has also been observed in MDD relative to controls [75], and thus seems regionally similar but more severe in anxious depression. However, less temporal and insula thinning relative to non-anxious MDD has also been observed [76,77]. Corticolimbic functional connectivity (FC) also seems to distinguish anxious from non-anxious depression. Both anxiety dimensions and comorbid anxiety within MDD were associated with increased FC between limbic-striatal and prefrontal regions [21*,78-81], although decreased fronto-striatal FC has also been observed [79]. These corticolimbic-striatal networks are involved in functions like emotion regulation, decision making, and salience processing, and have generally been associated with decreased FC in MDD relative to controls [82]. Opposing patterns may relate to distinct approach-avoidance-deficits in anxious versus non-anxious depression [17,83].

A conceptual approach was taken by Oathes et al [21*], who combined syndromal and dimensional measures of depression and anxiety. Fitting with previous literature, MDD diagnosis was associated with reduced FC between the ACC and striatum and limbic/paralimbic reactivity, whereas both GAD diagnosis and dimensional anxious arousal and distress levels were associated with increased ACC-striatal connectivity and limbic/paralimbic reactivity. Interestingly, the combination of MDD diagnosis and dimensional anxiety measures proved the best fit with FC patterns, whereas anxiety disorder diagnosis did not add to the model [21*]. This suggests that FC deficits associated with anxiety may vary with symptom-levels and are not diagnosis-specific.

Of note, the ACC, insula and other regions structurally and functionally implicated in anxious depression, also play a role in predicting depression course and treatment outcome [84-86]. Thus, the deficits observed in these regions may be linked to the more severe affective and cognitive symptoms and the more disadvantageous clinical outcomes observed in anxious depression.

Taken together, despite the limited number of neuroimaging and biological studies and various definitions and assessment of anxious depression, anxious depression seems to be associated with a distinct neurobiological profile, showing increased immune dysregulation, more severe thinning in temporal and prefrontal areas, and increased corticolimbic FC patterns compared to non-anxious MDD.
Conclusion

Evidence demonstrates that anxious depression is common and clinically relevant. Poorer clinical and treatment outcomes as well as distinct neurobiological correlates were observed in persons with anxious depression versus persons with ‘pure’ (non-anxious) depression. Though various definitions for anxious depression were related to these poorer findings, more research is needed to identify which underlying anxiety features captured in different anxious depression definitions are driving associations with clinical outcomes and biology. For this, a transdiagnostic approach such as the Research Domain Criteria (RDoC) may be useful [87]. This may help to identify specific neurobiological targets that can contribute to the improvement of treatments for anxious depressed patients.

Key points

▸ Despite heterogeneity in diagnostic criteria and assessment instruments, anxious depression is common: 42–78% of all depressed patients suffer from co-occurring anxiety.
▸ Patients with anxious depression have poorer clinical and treatment outcomes, and may therefore benefit from specific treatment strategies.
▸ Anxious depression seems to be associated with a distinct neurobiological profile with increased immune and hypothalamic-pituitary-adrenal (HPA)-axis dysregulations and brain abnormalities including more severe cortical thinning, and increased corticolimbic functional connectivity patterns, compared to non-anxious depression.
▸ The recently introduced DSM-5 5-item anxious distress specifier can adequately predict course and treatment outcomes, making it a potential quick and easy-to-use indicator to select the subgroup of anxious depression patients in need of novel or more intensive treatment and follow-up.
References

Papers of particular interest, published within the annual period of review, have been highlighted as:
* of special interest
** of outstanding interest

Chapter 5

* This is the first neuroimaging study combining dimensional and diagnostic measures of depression and anxiety. Their findings suggest that a combination of diagnostic MDD and dimensional anxiety symptom measures may best capture neural connectivity patterns in anxiety and depression.
* This is the first study to evaluate the longitudinal predictive validity of the DSM-5 anxious distress specifier in terms of clinical outcomes over 2 years in patients with MDD and compared it with that of comorbid DSM-IV-based anxiety disorder diagnoses. The anxious distress specifier is a welcome development in the field of anxious depression as it may be a clinically relevant measure to identify significant anxiety in MDD patients.
Patients with anxious depression

* This is the first study that compared the validity of a measure of the anxious distress specifier -the DSM-5 anxious distress specifier interview- with the HAM-A. The anxious distress interview appeared to be as valid as the HAM-A.


** This study investigated the differences in sociodemographic, clinical, and treatment characteristics between MDD patients with and without anxiety disorders. This is the first study itemizing according to the different subtypes of anxiety disorders.


Patients with anxious depression


