CNS Spectrums

www.cambridge.org/cns

Anxious distress in people with major depressive episodes: a cross-sectional analysis of clinical correlates

Francesco Bartoli[1], Bianca Bachi[1], Tommaso Callovini[1], Dario Palpella[1], Susanna Piacenti[1], Marco Morreale[1], Maria Elisa Di Lella[1], Cristina Crocamo[1], Giuseppe Carrà[1,2] and NOMIAC Investigators

[1]Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy and [2]Division of Psychiatry, University College London, London, UK

Original Research

Cite this article: Bartoli F, Bachi B, Callovini T, Palpella D, Piacenti S, Morreale M, Di Lella ME, Crocamo C, Carrà G, and NOMIAC Investigators (2024). Anxious distress in people with major depressive episodes: a cross-sectional analysis of clinical correlates. *CNS Spectrums* **29**(1), 49–53.
https://doi.org/10.1017/S1092852923002377

Received: 16 May 2023
Accepted: 14 July 2023

Keywords:
anxious distress; major depressive episode; major depressive disorder; bipolar disorder; mixed features

Corresponding author:
Francesco Bartoli;
Email: francesco.bartoli@unimib.it

NOMIAC Investigators include: Filippo Fabio Barbieri, Alessandra Bartoccetti, Carlo Bassetti, Gianna Bernasconi, Carlo Bommartini, Paolo Bona, Federica Boniello, Angela Calabrese, Aurelia Canestro, Chiara Alessandra Capogrosso, Daniele Cavaleri, Marta Castiglioni, Riccardo Matteo Cioni, Francesca Colangelo, Aldo De Pietra, Tommaso Frigeni, Marco Gazzola, Letizia Gianfelice, Nicole Gandolfo, Pierluca Guzzi, Giada Lauria, Serena Limonta, Susanna Lucini Paioni, Stefano Mauro, Martina Molendini, Pietro Morello, Federico Moretti, Christian Nasti, Luca Prestifilippo, Martina Re, Oliviero Villa (University of Milano-Bicocca), and Paolo Camera (ASST Nord Milano).

Abstract

Objective. Most people with major depressive episodes meet the criteria for the anxious distress (AD) specifier defined by DSM-5 as the presence of symptoms such as feelings of tension, restlessness, difficulty concentrating, and fear that something awful may happen. This cross-sectional study was aimed at identifying clinical correlates of AD in people with unipolar or bipolar depression.

Methods. Inpatients with a current major depressive episode were included. Data on socio-demographic and clinical variables were collected. The SCID-5 was used to diagnose depressive episodes and relevant specifiers. The Montgomery–Åsberg Depression Rating Scale (MADRS) and Young Mania Rating Scale (YMRS) were used to assess the severity of depressive and manic (mixed) symptoms, respectively. Multiple logistic regression analyses were carried out to identify clinical correlates of AD.

Results. We included 206 people (mean age: 48.4 ± 18.6 yrs.; males: 38.8%) admitted for a major depressive episode (155 with major depressive disorder and 51 with bipolar disorder). Around two-thirds of the sample (N = 137; 66.5%) had AD. Multiple logistic regression models showed that AD was associated with mixed features, higher YMRS scores, psychotic features, and a diagnosis of major depressive disorder ($p < 0.05$).

Conclusion. Despite some limitations, including the cross-sectional design and the inpatient setting, our study shows that AD is likely to be associated with mixed and psychotic features, as well as with unipolar depression. The identification of these clinical domains may help clinicians to better contextualize AD in the context of major depressive episodes.

Introduction

The combination of depression and anxiety, impacting individual outcomes and response to treatments of people with major depressive episodes, has been extensively explored.[1-3] Aiming at a more consistent definition of anxious depression,[4] the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), introduced the "anxious distress" (AD) specifier that can be applied to any depressive episodes in the context of both unipolar and bipolar disorders.[5] AD is defined by the presence of symptoms including feelings of tension, restlessness, difficulty concentrating, and fear that something awful may happen or to lose control. AD should be further evaluated according to its severity, based on the number of criteria.[5] The inclusion of AD as a specifier of mood episodes has stimulated research in this field over the last few years.[6,7] Data from the National Epidemiologic Survey on Alcohol and Related Conditions III highlighted that AD occurred in around 75% of people suffering from depression.[8] The AD specifier in unipolar and bipolar depression may be linked to peculiar clinical outcomes.[9,10] Longitudinal data showed that the AD specifier may significantly outperform anxiety disorders in predicting chronicity, time to remission, and functional disability of major depressive disorders.[11] Moreover, AD has been associated with an increased severity of depressive symptoms.[12-14] The clinical management of AD may be made more complex by its interconnection with mixed features, especially in people with bipolar disorder.[15,16] As a whole, the available literature seems to highlight that AD may identify a group of patients with a specific clinical profile.[13,14,17] Nonetheless, considering that studies in this field are sparse and influenced by a high degree of variability in terms of methodology and target populations, additional research is needed to identify key clinical variables associated with this condition. This study may be helpful to provide additional insight into the AD specifier in the context of unipolar and bipolar depression. We performed a cross-sectional study aimed at identifying clinical correlates of AD in people with major depressive episodes. We hypothesized that they would have higher clinical severity than those without AD,

© The Author(s), 2023. Published by Cambridge University Press. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (http://creativecommons.org/licenses/by/4.0), which permits unrestricted re-use, distribution and reproduction, provided the original article is properly cited.

in terms of both depressive and manic (mixed) symptoms, as well as for the occurrence of mixed features specifier.

Methods

This cross-sectional study was designed and reported in accordance with the "Strengthening the Reporting of Observational studies in Epidemiology (STROBE)" statement.[18] It was approved by the local Ethics Committee as a part of the broader Northern Milan Area Cohort (NOMIAC) project.[19]

Setting and eligibility criteria

We included individuals consecutively admitted for inpatient treatment from May 2020 to December 2022 to the psychiatric intensive care units (accounting for a total of 27 beds) of the local Nord Milano Mental Health Care Trust. This institution provides mental health care for about 270 000 inhabitants of the northern area of the Metropolitan City of Milan, from both deprived and affluent, highly urbanized districts. Subjects suffered from major depressive or bipolar disorders and were admitted for a major depressive episode as defined by the DSM-5 criteria. For study participants with multiple admissions, we used data from the first hospitalization. We excluded people i) younger than 16; ii) with intellectual disability; iii) with cognitive impairment or dementia; iv) with very brief hospital stays (<2 days).

Data collection

We collected information on socio-demographic characteristics, including age, gender, education, marital status, and employment. Data on clinical characteristics, including diagnosis, comorbid personality disorders, alcohol and substance use disorders, previous suicide attempts, physical diseases (diabetes, dyslipidemia, and hypertension), and psychopharmacological treatments at admission, were retrieved from clinical records and chart review. Trained assessors ("NOMIAC Investigators") used the Structured Clinical Interview for DSM-5 (SCID-5)[20] to identify individuals with a current major depressive episode, and related specifiers, including AD, mixed features, and psychotic features.

According to DSM-5, AD was defined by the presence of at least two of the following symptoms during the majority of days of the current 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.
5. Feeling that the individual might lose control of himself or herself.

The severity of AD was differentiated, according to the number of criteria met: mild (two criteria), moderate (three criteria), moderate–severe (four criteria), or severe (five criteria).[5] Depressive symptom severity was measured by the Montgomery–Åsberg Depression Rating Scale (MADRS). A MADRS item-10 score ≥ 2 was used to rate the presence of current suicidal ideation.[21,22] The Young Mania Rating Scale (YMRS) was used to assess symptoms of the opposite polarity (manic symptoms). Data were collected and recorded anonymously using a standardized extraction template.

Data analysis

Standard statistics were computed for descriptive purposes. To estimate the potential differences between individuals with and without AD, we firstly carried out relevant univariate analyses. We used the Pearson's Chi-square and Fisher's exact tests (according to the number of cases) for categorical variables, as well as Student's T or Mann–Whitney U tests (according to the data distribution) for continuous variables. Multiple logistic regression models were performed to assess the association between AD and candidate explanatory variables. These included age, gender, and diagnosis (major depressive versus bipolar disorder), as *a priori* characteristics, and those variables for which a p-value <0.1 was estimated at univariate analyses, consistently with the statistical approach used in previous studies.[23,24] Regression coefficients with related 95% Confidence Interval (95%CI) were used to estimate the effects of explanatory variables. Statistical significance was set at $p < 0.05$. Analyses were performed using the Stata statistical software package, release 17.

Results

Characteristics of study participants

Among 779 people admitted to the inpatient units during the study period, 206 participants reported a depressive episode and were included in this study (mean age ± SD: 48.4 ± 18.6 years; proportion of men: 38.8%). Among them, 155 individuals suffered from major depressive disorder and 51 from bipolar disorder (12 type-I, 18 type-II, and 21 unspecified bipolar disorder), respectively. Two-thirds of the sample (N = 137; 66.5%) showed AD (41 individuals mild, 72 moderate, 18 moderate–severe, and six severe AD). The sample characteristics are reported in Table 1.

Correlates of anxious distress: univariate analyses

Univariate analyses estimated that the AD specifier was associated with manic symptoms as measured by YMRS score ($p = 0.004$), though not with depressive symptom severity ($p = 0.35$). In addition, individuals with psychotic features were more likely to show AD ($p = 0.001$). No other variables, including the mixed features specifier ($p = 0.06$) and the occurrence of substance use disorders ($p = 0.09$), were associated with AD. Results are shown in Table 1.

Correlates of anxious distress: multiple logistic regression analyses

Considering the clinical overlap between manic symptoms as measured by YMRS and the mixed features specifier, we run two independent multiple logistic regression models, sequentially including these explanatory variables. The first (Model 1) showed that AD was associated with higher YMRS scores ($p = 0.004$), psychotic features ($p = 0.017$), and a diagnosis of major depressive disorder ($p = 0.001$). Similar findings emerged from the second model (Model 2), corroborating the association of AD with mixed ($p = 0.049$) and psychotic features ($p = 0.004$), and with a diagnosis of major depressive disorder ($p = 0.004$). Results are shown in Table 2.

https://doi.org/10.1017/S1092852923002377 Published online by Cambridge University Press

Table 1. Sample characteristics and differences between individuals with and without Anxious Distress

Variables	Overall sample (*N* = 206)	With anxious distress (*N* = 137)	Without anxious distress (*N* = 69)	Test statistic	*p*-value
Socio-demographic characteristics					
Age (years), mean ± SD	48.4 ± 18.6	48.7 ± 18.0	47.8 ± 19.9	z = −0.188	ns[a]
Male gender, *N* (%)	80 (38.8)	56 (40.9)	24 (34.8)	χ^2 = 0.717	ns[b]
Education (years), mean ± SD[c]	11.3 ± 3.3	11.2 ± 3.2	11.5 ± 3.4	z = 0.891	ns[a]
Clinical characteristics					
Major depressive disorder, *N* (%)	155 (75.2)	108 (78.8)	47 (68.1)	χ^2= 2.829	ns[b]
MADRS, mean ± SD	28.8 ± 7.9	29.1 ± 7.9	28.0 ± 7.8	t = −0.937	ns[d]
YMRS, mean ± SD	3.7 ± 5.2	4.5 ± 5.9	2.0 ± 2.9	z = −2.893	0.004[a]
Mixed features, *N* (%)	17 (8.3)	15 (10.9)	2 (2.9)	–	ns[e]
Psychotic features, *N* (%)	32 (15.5)	29 (21.2)	3 (4.3)	–	0.001[e]
Suicidal ideation, *N* (%)	128 (62.1)	81 (59.1)	47 (68.1)	χ^2 = 1.577	ns[b]
Personality disorder, *N* (%)	98 (47.6)	66 (48.2)	32 (46.4)	χ^2 = 0.059	ns[b]
Alcohol use disorder, *N* (%)	33 (16.0)	26 (19.0)	7 (10.1)	χ^2 = 2.661	ns[b]
Substance use disorder, *N* (%)	30 (14.6)	24 (17.5)	6 (8.7)	χ^2 = 2.871	ns[b]
Psychopharmacological treatment					
Antidepressants, *N* (%)	129 (62.6)	84 (61.3)	45 (65.2)	χ^2 = 0.299	ns[b]
Lithium, *N* (%)	25 (12.1)	14 (10.2)	11 (15.9)	χ^2 = 1.409	ns[b]
Anticonvulsants, *N* (%)	30 (14.6)	18 (13.1)	12 (17.4)	χ^2 = 0.667	ns[b]
First-generation antipsychotics, *N* (%)	20 (9.7)	13 (9.5)	7 (10.1)	χ^2 = 0.022	ns[b]
Second-generation antipsychotics, *N* (%)	93 (45.1)	62 (45.3)	31 (44.9)	χ^2 = 0.002	ns[b]
Cardiovascular risk factors					
Diabetes, *N* (%)	16 (7.8)	11 (8.0)	5 (7.2)	χ^2 = 0.039	ns[b]
Dyslipidemia, *N* (%)	29 (14.1)	19 (13.9)	10 (14.5)	χ^2 = 0.015	ns[b]
Hypertension, *N* (%)	46 (22.3)	31 (22.6)	15 (21.7)	χ^2 = 0.021	ns[b]

Abbreviations: MADRS, Montgomery–Åsberg depression rating scale; N, number of subjects; ns, not significant; SD, standard deviation; YMRS, Young Mania rating scale.
[a]Mann–Whitney test.
[b]Pearson's Chi-square test.
[c]Missing data: *N* = 8 (4 with anxious distress, 4 without anxious distress).
[d]Student's *T* test.
[e]Fisher's exact test.

Discussion

The aim of this study was to investigate the clinical correlates of AD among people with unipolar and bipolar depression consecutively admitted for inpatient care. Benefitting from standardized assessments and rigorous sampling procedures, we hypothesized that people with AD would have higher clinical severity than those without AD in terms of both depressive and manic (mixed) symptoms, as well as for the occurrence of mixed features specifier.

We found that AD occurs in two out of three people with unipolar or bipolar depression. Although prevalence rates are slightly lower than those estimated in previous studies, based on different geographical areas and clinical settings,[8,12,25] several findings characterizing AD in people with unipolar or bipolar depression emerged from our study.

First, people with AD had more symptoms of the opposite polarity (mixed features specifier and manic symptoms as measured by YMRS) than those without AD, regardless of age, gender, and diagnosis. This is not surprising and seems consistent with evidence emerging from previous studies.[10,26] Indeed, the so-called mixed depression seems more likely to occur in people suffering from a major depressive episode with AD.[9] It has been shown that the interplay between anxiety and manic symptoms in the context of depression represents an important clinical domain, influencing treatment response and disease course.[26,27] Nonetheless, the partial overlap between anxious and manic symptoms remains a matter of debate, making the differentiation of these clinical domains complex.[17] Clinical features, such as racing thoughts and pressured speech, may be common in both AD and manic symptoms.[17] In addition, the combination of anxiety and mixed features in depression may be the possible expression of a painful inner tension or, on the other side, a disinhibited goal-directed behavior and thought.[28]

Secondly, we uncovered a strong link between AD and psychotic features. To our knowledge, this is the first study ascertaining this association. This finding is particularly relevant considering the impact of anxiety on treatment outcomes of psychotic depression.[29] It should be noted that, although psychotic-like experiences are usually associated with psychotic disorders, these symptoms are frequent among individuals with either depression or anxiety.[30] Even

https://doi.org/10.1017/S1092852923002377 Published online by Cambridge University Press

Table 2. Factors associated with Anxious Distress in people with Major Depressive Episodes: Multiple Logistic Regression Models

Variables	Model 1 coeff. [95%CI]	Model 2 coeff. [95%CI]
Age[a]	−0.003 [−0.020 to 0.015] z = −0.31, p = 0.757	0.001 [−0.016 to 0.018] z = 0.12, p = 0.902
Male gender[b]	0.225 [−0.424 to 0.873] z = 0.68, p = 0.497	0.225 [−0.413 to 0.864] z = 0.69, p = 0.489
Major depressive disorder[c]	1.302 [0.501 to 2.104] z = 3.19, p = 0.001	1.147 [0.377 to 1.916] z = 2.92, p = 0.004
YMRS[a]	0.138 [0.045 to 0.230] z = 2.92, p = 0.004	–
Mixed features[d]	–	1.629 [0.004 to 3.254] z = 1.96, p = 0.049
Psychotic features[e]	1.614 [0.295 to 2.934] z = 2.40, p = 0.017	1.902 [0.608 to 3.196] z = 2.88, p = 0.004
Substance use disorder[f]	0.578 [−0.454 to 1.610] z = 1.10, p = 0.272	0.587 [−0.426 to 1.601] z = 1.14, p = 0.256

Abbreviations: CI, confidence interval; coeff., regression coefficient; YMRS, Young Mania rating scale.
[a]for a 1-unit change.
[b]vs. female gender.
[c]vs. bipolar disorder.
[d]vs. without mixed features.
[e]vs. without psychotic features.
[f]vs. without substance use disorder.

though the mechanisms underlying psychotic features and anxiety remain unknown,[31] it can be hypothesized that anxiety may represent an individual response to the feeling of unreality and dissociative experiences[32] that may precede delusions and hallucinations emerging from a depressive state. Clearly, the cross-sectional design of our study did not allow us to analyze the temporal sequence of these clinical domains. Nonetheless, the co-occurrence of psychosis and anxiety in depression strengthens the concept that specific networks of symptoms from different psychopathological dimensions may mutually influence each other.[33]

Moreover, from our study, AD seems to be associated with a diagnosis of major depressive disorder, when controlling for putative variables (age, gender, mixed and psychotic features). Thus, our findings seem to support the hypothesis that AD may be a peculiar specifier of unipolar depression,[26] instead of a potential bipolarity index of major depressive episodes,[10] which was an alternative hypothesis from previous conflicting evidence.

Finally, our study showed that AD might be unrelated to other clinical variables. In particular, it is worth mentioning that no association between depressive symptom severity and AD was estimated. This is not consistent with findings from relevant previous studies.[14,16] Nonetheless, it should be considered that individuals included in our study were enrolled from inpatient units, where only people with a severe clinical condition are admitted, thus making it difficult to find possible differences in inevitably high symptom severity.

Some limitations should be acknowledged when interpreting our findings. First, the cross-sectional design of our study did not allow us to make any inference on the causal relationship between AD and the explored clinical domains of major depressive episodes. Second, since our study was based on a relatively limited sample without any size estimation, we should not rule out further associations between putative variables and AD, possibly not detected by our analyses. This may also explain the lack of precision for some explanatory variables (eg, mixed and psychotic features). Third, the study recruitment from an inpatient setting makes it likely to oversample individuals with increased care needs and poorer global functioning. These subjects may not be representative of the overall clinical population with depression. In addition, we did not assess affective temperaments despite their potential influence on mood disorder course and severity.[34] Similarly, we did not report information on lifetime history of suicidal attempts, due to the high risk of recall bias. Finally, our study assumed just a categorical perspective for AD as well as for covariates, such as substance use and personality disorders, since the relatively small sample size did not allow us to consider their severity. Additional studies are needed to analyze whether putative clinical variables correlate with AD severity. These should also clarify whether the intolerance of uncertainty might further add to a more fine-grained pattern of AD.[35-37]

Conclusion

Our study provides additional insight into the clinical profile of individuals with AD in the context of depression. It seems associated with major depressive disorder and clinical domains, including mixed and psychotic features, though not with depressive symptom severity. Additional studies are needed to explore the generalizability of our findings and to better contextualize AD in the context of major depressive episodes.

Author contribution. Investigation: B.B., D.P., M.M., S.P., T.C.; Resources: B.B., D.P., M.E.D.L., M.M., S.P., T.C., F.B.; Visualization: B.B., C.C., M.E.D.L., F.B.; Writing – review & editing: B.B., C.C., D.P., G.C., M.E.D.L., M.M., S.P., T.C.; Data curation: C.C., D.P., M.E.D.L., S.P., T.C.; Formal analysis: C.C., G.C., F.B.; Methodology: C.C., F.B.; Software: C.C., F.B.; Conceptualization: G.C., F.B.; Supervision: G.C., F.B.; Project administration: F.B.; Validation: F.B.; Writing – original draft: F.B.

Financial support. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure. The authors do not have anything to disclose.

References

1. Fava M, Rush AJ, Alpert JE, et al. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. *Am J Psychiatry*. 2008;**165**(3):342–351. doi:10.1176/appi.ajp.2007.06111868.
2. Dold M, Bartova L, Souery D, et al. Clinical characteristics and treatment outcomes of patients with major depressive disorder and comorbid anxiety disorders - results from a European multicenter study. *J Psychiatr Res*. 2017; **91**:1–13. doi:10.1016/j.jpsychires.2017.02.020.
3. Gaspersz R, Nawijn L, Lamers F, Penninx BWJH. Patients with anxious depression: overview of prevalence, pathophysiology and impact on course and treatment outcome. *Curr Opin Psychiatry*. 2018;**31**(1):17–25. doi: 10.1097/YCO.0000000000000376.
4. Ionescu DF, Niciu MJ, Henter ID, Zarate CA. Defining anxious depression: a review of the literature. *CNS Spectr*. 2013;**18**(5):252–260. doi:10.1017/S1092852913000114.
5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Arlington, WA: American Psychiatric Association; 2013. doi:10.1176/appi.books.9780890425596.
6. Zimmerman M, Clark H, McGonigal P, Harris L, Guzman Holst C, Martin J. Relationship between the DSM-5 anxious distress specifier and the Hamilton depression rating scale anxiety/somatization factor. *J Nerv Ment Dis*. 2018;**206**(2):152–154. doi:10.1097/NMD.0000000000000767.
7. Zimmerman M, Kerr S, Balling C, Kiefer R, Dalrymple K. DSM-5 anxious distress specifier in patients with bipolar depression. *Ann Clin Psychiatry*. 2020;**32**(3):157–163.

8. Hasin DS, Sarvet AL, Meyers JL, et al. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. *JAMA Psychiatry.* 2018;**75**(4):336–346. doi:10.1001/jamapsychiatry.2017.4602.
9. Takeshima M. Anxious distress in monopolar and bipolar depression: Clinical characteristics and relation with mixed depression in Japan. *Psychiatry Clin Neurosci.* 2018;**72**(6):456–457. doi:10.1111/pcn.12660.
10. Tundo A, Musetti L, de Filippis R, et al. Is there a relationship between depression with anxious distress DSM-5 specifier and bipolarity? A multicenter cohort study on patients with unipolar, bipolar I and II disorders. *J Affect Disord.* 2019;**245**:819–826. doi:10.1016/j.jad.2018.11.024.
11. Gaspersz R, Lamers F, Kent JM, et al. Longitudinal predictive validity of the DSM-5 anxious distress specifier for clinical outcomes in a large cohort of patients with major depressive disorder. *J Clin Psychiatry.* 2017;**78**(2): 207–213. doi:10.4088/JCP.15m10221.
12. Maneeton N, Suttajit S, Maneeton B, et al. Clinical and socio-demographic correlates of anxious distress in Asian outpatients with major depressive disorder. *Nord J Psychiatry.* 2017;**71**(7):503–508. doi:10.1080/08039488.2017.1335344.
13. Otsubo T, Hokama C, Sano N, Watanabe Y, Kikuchi T, Tanaka K. How significant is the assessment of the DSM-5 'anxious distress' specifier in patients with major depressive disorder without comorbid anxiety disorders in the continuation/maintenance phase? *Int J Psychiatry Clin Pract.* 2021;**25**(4):385–392. doi:10.1080/13651501.2021.1907415.
14. Rosellini AJ, Bourgeois ML, Correa J, Tung ES, Goncharenko S, Brown TA. Anxious distress in depressed outpatients: prevalence, comorbidity, and incremental validity. *J Psychiatr Res.* 2018;**103**:54–60. doi:10.1016/j.jpsychires.2018.05.006.
15. Bartoli F, Crocamo C, Carrà G. Clinical correlates of DSM-5 mixed features in bipolar disorder: a meta-analysis. *J Affect Disord.* 2020;**276**:234–240. doi:10.1016/j.jad.2020.07.035.
16. Sugawara H, Tsutsumi T, Inada K, et al. Association between anxious distress in a major depressive episode and bipolarity. *Neuropsychiatr Dis Treat.* 2019;**15**:267–270. doi:10.2147/NDT.S188947.
17. Tundo A, Musetti L, Del Grande C, et al. The relationship between depression with anxious distress DSM-5 specifier and mixed depression: a network analysis. *CNS Spectr.* 2021;**26**(3):251–257. doi:10.1017/S1092852920000085.
18. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol.* 2008;**61**(4):344–349. doi:10.1016/j.jclinepi.2007.11.008.
19. Bartoli F, Bachi B, Calabrese A, et al. Effect of long-acting injectable antipsychotics on emergency department visits and hospital admissions in people with bipolar disorder: a retrospective mirror-image analysis from the Northern Milan Area Cohort (NOMIAC) study. *J Affect Disord.* 2022;**318**:88–93. doi:10.1016/j.jad.2022.08.096.
20. First MB, Williams JBW, Karg RS, Spitzer RL. *User's Guide for the SCID-5-CV Structured Clinical Interview for DSM-5® Disorders: Clinical Version*. Washington, DC: American Psychiatric Publishing, Inc.; 2016.
21. Ballard ED, Luckenbaugh DA, Richards EM, et al. Assessing measures of suicidal ideation in clinical trials with a rapid-acting antidepressant. *J Psychiatr Res.* 2015;**68**:68–73. doi:10.1016/j.jpsychires.2015.06.003.
22. Feeney A, Hock RS, Freeman MP, et al. The effect of single administration of intravenous ketamine augmentation on suicidal ideation in treatment-resistant unipolar depression: Results from a randomized double-blind study. *Eur Neuropsychopharmacol.* 2021;**49**:122–132. doi:10.1016/j.euroneuro.2021.04.024.
23. Bartoli F, Cavaleri D, Moretti F, et al. Pre-discharge predictors of 1-year rehospitalization in adolescents and young adults with severe mental disorders: a retrospective cohort study. *Medicina (Kaunas).* 2020;**56**(11): 613 doi:10.3390/medicina56110613.
24. Clerici M, Bartoli F, Carretta D, Crocamo C, Bebbington P, Carrà G. Cardiovascular risk factors among people with severe mental illness in Italy: a cross-sectional comparative study. *Gen Hosp Psychiatry.* 2014;**36**(6): 698–702. doi:10.1016/j.genhosppsych.2014.08.005.
25. Zimmerman M, Martin J, McGonigal P, et al. Validity of the DSM-5 anxious distress specifier for major depressive disorder. *Depress Anxiety.* 2019;**36**(1):31–38. doi:10.1002/da.22837.
26. Shim IH, Lee J, Kim MD, et al. The prevalence and diagnostic classification of mixed features in patients with major depressive episodes: a multicenter study based on the DSM-5. *Int J Methods Psychiatr Res.* 2019;**28**(3):e1773. doi:10.1002/mpr.1773.
27. Shim IH, Bae DS, Bahk WM. Anxiety or agitation in mood disorder with mixed features: a review with a focus on validity as a dimensional criterion. *Ann Clin Psychiatry.* 2016;**28**(3):213–220.
28. Swann AC. Activated depression: mixed bipolar disorder or agitated unipolar depression? *Curr Psychiatry Rep.* 2013;**15**(8):376. doi:10.1007/s11920-013-0376-1.
29. Davies SJ, Mulsant BH, Flint AJ, et al. Differential impact of anxiety symptoms and anxiety disorders on treatment outcome for psychotic depression in the STOP-PD study. *Compr Psychiatry.* 2014;**55**(5): 1069–1076. doi:10.1016/j.comppsych.2014.02.001.
30. Varghese D, Scott J, Welham J, et al. Psychotic-like experiences in major depression and anxiety disorders: a population-based survey in young adults. *Schizophr Bull.* 2011;**37**(2):389–393. doi:10.1093/schbul/sbp083.
31. Saha S, Scott J, Varghese D, McGrath J. Anxiety and depressive disorders are associated with delusional-like experiences: a replication study based on a National Survey of Mental Health and Wellbeing. *BMJ Open.* 2012;**2**(3): e001001. doi:10.1136/bmjopen-2012-001001.
32. Černis E, Freeman D, Ehlers A. Describing the indescribable: a qualitative study of dissociative experiences in psychosis. *PLoS One.* 2020;**15**(2): e0229091. doi:10.1371/journal.pone.0229091.
33. Wigman JT, van Nierop M, Vollebergh WA, et al. Evidence that psychotic symptoms are prevalent in disorders of anxiety and depression, impacting on illness onset, risk, and severity--implications for diagnosis and ultra-high risk research. *Schizophr Bull.* 2012;**38**(2):247–257. doi:10.1093/schbul/sbr196.
34. Simonetti A, Luciano M, Sampogna G, et al. Effect of affective temperament on illness characteristics of subjects with bipolar disorder and major depressive disorder. *J Affect Disord.* 2023;**334**:227–237. doi:10.1016/j.jad.2023.04.130.
35. Koerner N, Mejia T, Kusec A. What's in a name? Intolerance of uncertainty, other uncertainty-relevant constructs, and their differential relations to worry and generalized anxiety disorder. *Cogn Behav Ther.* 2017;**46**(2): 141–161. doi:10.1080/16506073.2016.1211172.
36. Probert-Lindström S, Perrin S. An examination of distress tolerance, anxiety sensitivity, and intolerance of uncertainty in adults in routine psychiatric care. *Acta Psychol (Amst).* 2023;**235**:103902. doi:10.1016/j.actpsy.2023.103902.
37. Sabouri S, Gerber M, Lemola S, et al. Examining dark triad traits in relation to sleep disturbances, anxiety sensitivity and intolerance of uncertainty in young adults. *Compr Psychiatry.* 2016;**68**:103–110. doi: 10.1016/j.comppsych.2016.03.012.

https://doi.org/10.1017/S1092852923002377 Published online by Cambridge University Press