Title

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Journal

The American Journal of Geriatric Psychiatry, 30(10)

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Publication Date

2022-10-01

DOI

10.1016/j.jagp.2022.03.007

HHS Public Access

Author manuscript

Am J Geriatr Psychiatry. Author manuscript; available in PMC 2023 October 01.

Published in final edited form as:

Am J Geriatr Psychiatry. 2022 October ; 30(10): 1096–1107. doi:10.1016/j.jagp.2022.03.007.

Symptom Severity Mixity in Older-age Bipolar Disorder: Analyses from the Global Aging & Geriatric Experiments in Bipolar Disorder Database (GAGE-BD)

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All authors made a substantive contribution to the study design as described below. LTE contributed to the design, data acquisition, analysis, interpretation, drafting, final approval, and accountability of the study. FBSB contributed to analysis, interpretation, revision, final approval, and accountability of the study. AD contributed to the design, data acquisition, interpretation, revision, final approval, and accountability of the study. SR contributed to the design, data acquisition, interpretation, revision, final approval, and accountability of the study. OPA contributed to the data acquisition, interpretation, revision, final approval, and accountability of the study. AJMB contributed to the interpretation, revision, final approval, and accountability of the study. HPB contributed to the data acquisition, interpretation, revision, final approval, and accountability of the study. BPF contributed to the data acquisition, interpretation, revision, final approval, and accountability of the study. REP contributed to the interpretation, revision, final approval, and accountability of the study. OVF contributed to the design, data acquisition, interpretation, revision, final approval, and accountability of the study. AG contributed to the data acquisition, interpretation, revision, final approval, and accountability of the study. EJ contributed to the interpretation, revision, final approval, and accountability of the study. EV contributed to the data acquisition, interpretation, revision, final approval, and accountability of the study. BM contributed to the data acquisition, interpretation, revision, final approval, and accountability of the study. SiS contributed to the data acquisition, interpretation, revision, final approval, and accountability of the study. NPGP contributed to the interpretation, revision, final approval, and accountability of the study. SeS contributed to the data acquisition, interpretation, revision, final approval, and accountability of the study. AS contributed to the data acquisition, interpretation, revision, final approval, and accountability of the study. ST contributed to the data acquisition, interpretation, revision, final approval, and accountability of the study. MS contributed to the design, data acquisition, interpretation, revision, drafting, final approval, and accountability of the study.

The remaining authors report no conflicts with any product mentioned or concept discussed in this article.

Data Statement

The data has not been previously presented orally or by poster at scientific meetings.

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Abstract

Objective: Some individuals with bipolar disorder (BD) experience manic and depressive symptoms concurrently, but data are limited on symptom mixity in older-age bipolar disorder (OABD). Using the Global Aging & Geriatric Experiments in Bipolar Disorder Database, we characterized mixity in OABD and associations with everyday function.

Methods: The sample (n=805), from 12 international studies, included cases with both mania and depression severity ratings at a single timepoint. Four mixity groups were created: asymptomatic (A), mixed (Mix), depressed only (Dep) and manic only (Man). Generalized linear mixed models used mixity group as the predictor variable; cohort was included as a random intercept. Everyday function was assessed with the Global Assessment of Functioning score.

Results: Group proportions were Mix (69.6%; n=560), followed by Dep (18.4%; n=148), then A (7.8%; n=63), then Man (4.2%; n= 34); levels of depression and mania were similar in Mix compared to Dep and Man, respectively. Everyday function was lowest in Mix, highest in A, and intermediate in Man and Dep. Within Mix, severity of depression was the main driver of worse functioning. Groups differed in years of education, with A higher than all others, but did not differ by age, gender, employment status, BD sub-type, or age of onset.

Conclusions: Mixed features predominate in a cross-sectional, global OABD sample and are associated with worse everyday function. Among those with mixed symptoms, functional status relates strongly to current depression severity. Future studies should include cognitive and other biological variables as well as longitudinal designs to allow for evaluation of causal effects.

Keywords

bipolar disorder; geriatric; elderly; mania; depression

OBJECTIVE

Bipolar disorder (BD) is characterized by two distinct types of mood symptoms, depression and mania/hypomania. However, some individuals with BD experience a ‘mixed’ state in which manic or hypomanic and depressive symptoms are present concurrently. The most recent version of the American Psychiatric Association’s Diagnostic and Statistical Manual (DSM-5) includes a ‘with mixed features’ specifier that applies to a manic or hypomanic episode with three or more depressive symptoms (or to a depressive episode with three or more manic symptoms) (1). Patients with Type I BD mixed symptoms have been noted to have a worse clinical course than those with ‘pure’ manic states, including more mood episodes, episodes of longer duration, and greater risk of suicidality (2).

Previous work suggests relatively minor differences in the mood symptom presentation of older versus younger patients with BD (3, 4). Few studies have specifically examined mixed states in older adults with bipolar disorder (OABD), however, and little is known about how common such states are in late life and how they relate to functioning in this group. The link between mixed features and circadian rhythms and sleep (5) in tandem with well-known age-related changes in sleep and rhythms and increased incidence of sleep disorders (6) suggest that mixity might increase with age. It also seems reasonable to predict

that depressive symptoms might predominate over mania symptoms in OABD compared to younger BD patients, given the known link between late-life depression symptoms and white matter hyperintensities (7), which are also seen in OABD, particularly those with a later age of onset (8). Finally, given the association of mixed symptoms with worse outcomes in BD (5), which has mostly been examined in younger samples, it seems reasonable to examine mixity as a possible predictor of functional outcomes in OABD.

The Global Aging & Geriatric Experiments in Bipolar Disorder Database (GAGE-BD), is a large integrated sample comprising archival studies being used to advance understanding of OABD (9). Previous work suggested a possible attenuation of both depressive and manic symptom severity with age (10), and a strong association of depression symptom severity with functional outcomes. However, the relative severity of mania and depression within individuals has not been examined, nor has the association of mixity with functioning. In the present study, we sought to get a better picture of age-relationships to mixity and relative symptom severity and the association of mixity with functioning in OABD. In this analysis, we created four subgroups of patients based on relative current mania and depression symptom severity: asymptomatic (A), mixed (Mix), depressed only (Dep), and manic only (Man). We hypothesized that older patients would be more likely to fall into the Dep and Mix subgroups compared to younger patients, and that functioning would be more impaired among participants in Mix compared with the other groups. We also explored whether there were any other demographic (e.g., gender, education, employment status) or clinical (age of onset, bipolar subtype) differences between mixity groups.

METHODS

Samples

We analyzed cross-sectional, multisite data from Wave 1 (as of March 2020) of the GAGE-BD integrated dataset. The project has been described previously (9) and details about each of the samples included in the first wave of the dataset, including the sample characteristics and meta-data about the contributing studies, have been reported elsewhere (10). Participants with BD were included in the present analysis if data on both mania severity and depression severity at a single timepoint were available (n=805). A total of 12 samples from 9 sites contributed data to this analysis: *Lady Davis Institute*'s 'Atorvastatin for the Treatment of Lithium-Induced Nephrogenic Diabetes Insipidus: A Randomized Controlled Trial' study (Atorvastatin; n=6); *Case Western Reserve University*'s 'Asenapine in the Treatment of Older Adults with Bipolar Disorder' study (OPT-BD; n=16), 'Ziprasidone Switching in Response to Adherence in Psychotropic-related Weight Gain Concerns among Patients with Bipolar Disorder' study (ZIP-AD; n=30), 'Open-label, Prospective Trial of Lamotrigine for Symptoms of Geriatric Bipolar Depression' study (GERI-SAD; n=44), and the multi-site 'Treatment Adherence Enhancement in Bipolar Disorder' study (CAE; n=184); *McLean Hospital*'s 'Geriatric Psychiatry Mood Disorders Research Database' (GMDD; n=37); *Center for Addiction & Mental Health*'s 'Cognition in Euthymic Older Adults with Bipolar Disorder' study (Cog-BD; n=48), *Taipei Medical University*'s Study 1 (TMU1; n=56), *University of California San Diego*'s 'Dynamic Inflammatory and Mood Predictors of Cognitive Aging in Bipolar Disorder' study (Inflammaging; n= 64), *Yale University*'s

'Mood Disorders Research Program Database' (Yale; n=84), *University of Pittsburgh Medical Center*'s 'The Effect of Bipolar Disorder and its Comorbidities on Cognition in Older Adults' study (UPMC; n=104), and *University of Barcelona*'s Bipolar Disorder Program Cohort (UBBDPC; n=132). Approval to contribute data was obtained by each site's institutional review boards or ethics committees and by the GAGE-BD coordinating center (Case Western Reserve University School of Medicine, Cleveland, Ohio, USA). Supplemental Table 1 shows the inclusion/exclusion criteria for the 12 studies from which our data were derived.

Measures

As previously described (10), demographic characteristics (age, gender, education, and employment status) and clinical data (diagnosis, BD subtype, age of onset, depression severity, and mania severity) were harmonized across studies. For mania severity, the Young Mania Rating Scale (11) was used by all included studies. For depression severity, some studies used the Hamilton Depression Rating Scale (HAM-D) (12) and others the Montgomery-Asberg Depression Rating Scale (MADRS) (13), so a 3-level depression severity score was created informed by published cut-off scores and the distribution of scores in the dataset: 0 = Absent depression (HAM-D or MADRS = 0), 1 = Lower depression (HAM-D = 1–16 or MADRS = 1– 19), 2 = Higher depression (HAM-D ≥ 17 or MADRS ≥ 20 (14, 15). The sample sizes and mean ± SD depression severity scores for the respective categories were: n=98 (HAM-D: 0.0±0.0; MDRS: 0.0±0.0), n=535 (HAM-D: 4.0±4.4; MDRS: 7.9±2.0), n=179 (HAM-D: 19.1±3.7; MDRS: 28.2±4.4).

To create mixity groups based on the within-subject pattern of current BD symptom severity, we also created a 3-level severity category for mania, based on YMRS total scores. The cutoffs we used were informed by our sample distribution (i.e., we desired to have adequate sample size in each category) and a consensus statement of experts in BD (16). The resulting categories were as follows: 0 = Absent mania (YMRS = 0), 1 = Lower mania (YMRS=1–4), and 2 = Higher mania (YMRS ≥ 5). Note that the terms lower and higher mania refer to the relative severity within our sample, not to absolute clinical significance of the symptoms. The respective sample sizes and YMRS score mean ±SD and range for these categories were, respectively: n=211 (0.0±0.0; 0–0), n=253 (2.36±1.1; 1–4), and n=341 (9.70±5.0; 5–44). We then created the four mixity groups from the intersection of the mania and depression 3-level categories of current mood symptoms. Individuals in the A group had scores of 0 for both mania and depression. Individuals in the Mix group had either lower depression + lower mania, lower depression + higher mania, lower mania + higher depression, or lower mania + higher depression. Individuals in the Man group had absent depression + lower mania or absent depression + higher mania; Individuals in the Dep group had either absent mania + lower depression or absent mania + higher depression.

Everyday functioning, our primary outcome measure, was assessed using the Global Assessment of Functioning (GAF) (17).

Statistical Analyses

To compare mixity groups on all variables, we used generalized linear mixed models with mixity group (4 categories) as the predictor variable. Continuous dependent variables (i.e., age, GAF, age of onset, education, YMRS), were checked for normality and transformed if necessary; log transformation of YMRS scores improved indices of normality. Within the linear mixed models, an identity link function was employed for continuous outcome variables; for discrete variables (e.g., gender, employment status, bipolar subtype, 3-level depression and mania severity categories) a binomial or multinomial distribution and logit link function was used. Our primary dependent measures were age and GAF; other analyses were exploratory. Cohort (study sample) was included as a random intercept to account for meta-data differences between the contributing studies. All analyses were carried out in IBM SPSS version 28. For all analyses, a two-sided alpha of 0.05 was considered statistically significant.

RESULTS

Demographic and clinical descriptive summary:

Table 1 shows descriptive variables for the total sample and the four mixity groups along with the results from the linear mixed model comparing the groups. The overall sample had an average age in the mid 50's, a higher proportion of women than men, slightly more than high school level education, and about a quarter were employed. Total YMRS average score was approximately 5. The majority of individuals scored in the lower severity harmonized depression category. GAF score was available in a subset of 439 participants; the average value was 61.1±12.8, indicating mild to moderate difficulties with everyday function.

As seen in Table 1 and Figure 1, the most frequently observed mixity group in our global, multi-site OABD sample was Mix (69.6%; n=560), followed by Dep (18.4%; n=148), then A (7.8%; n=63), then Man (4.2%; n= 34). Among those in the Mix group, individuals had either lower depression + lower mania (34.6%; n=194), lower depression + higher mania (35.7%; n=200), higher depression + lower mania (7.1%; n=40), or higher depression + higher mania (22.5%; n=126). In the Dep group, individuals had either lower depression + absent mania (92.6%; n=137) or higher depression + absent mania (7.4%; n=11). In the Man group, individuals had either absent depression + lower mania (55.9%, n=19) or absent depression + higher mania (44.1%; n=15).

Symptomatic clinical presentation:

Manic symptoms of higher severity (i.e., total YMRS score of 5 or higher), were found in 42.3% (n=342) of the entire sample of 805 BD cases. Depressive symptoms of higher severity (i.e., HAM-D score of at least 17 or MADRS score of at least 20), were found in 22% (n=177) of the entire sample. Among the 126 individuals with concurrent higher manic and higher depressive symptoms (15.7% of the entire sample), Table 2 shows the top 5 symptom domains identified on the YMRS, HAM-D and MADRS. The most common manic symptoms were language/thought disorder and irritability and the most common depressive symptoms were concentration problems, sadness, and anxiety.

Relationship to primary dependent variables:

Since study cohorts (samples) differed in the proportion of each mixity group (data not shown), we accounted for the cohort structure of the data in all models. Mixity groups did not differ in age (F[3,800]=.339, p=.80; Supplemental Table 2a). GAF scores, however, were significantly different between groups (F[3,435]=16.1, p=<0.001; Supplemental Table 2b). Pairwise comparisons showed that Mix had worse everyday function than all other groups, A had the best functioning, and Dep and Man were intermediate and not different from each other (Figure 2). The differences in functioning between the Mix group and the two unipolar groups (Dep and Man) did not appear to be due to the Mix group being more severe on either pole: Mix did not differ significantly from Man in level of mania (F[1,592]=.066, p=.80) or from Dep in proportions of each depression severity category (F[6,797]=.819, p=.555). Follow-up analyses only within the Mix group predicting GAF in a model with both 3-level depression and 3-level mania revealed that the main driver of poor functioning in this group was the severity of depression (F[1,340]=56.9, p<0.001), not severity of mania (F[1,340]=1.2, p=.274; Supplemental Table 2c).

Exploratory analyses:

We found that education level differed by mixity group (F[3,658]=3.6, p=.014); specifically, education was higher in the A group than all others (Supplemental Table 2d and Supplemental Figure 1). This finding was in the context of controlling for substantial site differences in educational attainment, particularly among the 6 sites that contributed participants in the A group (CAMH, UCSD, TMU, McLean, Barcelona, Yale). Mixity groups did not differ on any other explored variables, including gender (F[3,800]=.23, p=.87), employment status (F[3,564]=.32, p=.81), bipolar subtype (F[3,674]=.191, p=.903), or age of onset (F[3,646]=.94, p=.42).

CONCLUSIONS

Previous comprehensive reviews have documented the wide-spread occurrence of concurrent manic and depressive symptoms in people with BD and the likelihood of repeated episodes with poor symptomatic and functional recovery seen among those with mixed symptoms (5, 18). In our multi-national sample of over 800 BD cases, with a good representation of individuals aged 50 years and older and adequate gender balance, mixed manic and depressive symptoms of varying severity were relatively common (70%). The definition and conceptualization of mixed states has varied over time, but was substantially modified in DSM-5, requiring the presence of only three symptoms of the opposite mood polarity to qualify for the specifier “with mixed features” (1). Of note, this specifier could be used for a full-blown manic episode in BD type I, hypomanic episodes in Type I or Type II BD, as well as for a depressive episode in major depressive disorder (MDD) (19). Nearly 16% of individuals in our predominantly OABD sample had concurrent manic and depressive symptoms of higher severity. This is similar to the rate (14.3%) of mixed features based on the DSM-5 criteria observed in a multi-center study that included adults with BD of all ages (20). Among those with the most severe concurrent manic and depressive symptoms, language/thought disorder and irritability predominated as manic symptoms while concentration problems, sadness, and anxiety predominated as depressive symptoms.

Contrary to our initial hypothesis, we did not find that older participants were more likely to fall in the subgroups characterized by current depression symptoms (Mix and Dep), as there was no association of mixity group with age. In our previous work with the GAGE-BD sample, we observed lower depression severity and lower mania severity with older age; the present results further suggest that older BD patients do not have less mixity of symptom presentation nor are they more likely to show one pole of symptoms relative to the other or to be completely asymptomatic. Further longitudinal study will be necessary to understand the evolution of mixed symptoms within individuals across later-lite.

Importantly, consistent with our prediction and the literature on younger and multi-age samples (5), we found that the subgroup with mixed manic and depressive symptoms had the worst functioning, groups with only depression or mania symptoms were intermediate and similar to each other, and the A group was the least functionally impaired. Our results suggest that mixity itself is an important correlate of functioning above and beyond the severity of either mood pole alone, especially since the Mix subgroup was not more severe in depression than the Dep group nor were they more severe in mania than the Man group. However, among those with mixed symptoms, the severity of their depressive symptoms was more related to functioning than the severity of their mania symptoms. This is consistent with our previous findings showing a strong relationship of depression, but not mania, symptoms to functioning when these were considered independently in the whole GAGE-BD sample (10). The importance of depression symptoms over other symptoms to functioning is also in line with recent findings that residual depression is one of the strongest predictors of functioning among euthymic BD (21). Thus, OABD patients who present with mixed symptoms, especially those with higher severity of depressive than manic symptoms in the mix, are likely to have the poorest functional status. These data emphasize the importance of clinically addressing depressive symptoms in OABD particularly when symptoms of mania are also present in order to potentially improve functioning and overall recovery. In our exploration of other demographic and clinical variables that might be associated with mixed features and using generalized linear mixed models, only education was significantly associated, with higher levels of education seen in the A group compared to others. This might suggest that OABD who are more educated have better health literacy and perhaps are better equipped to advocate for high-quality care that helps them achieve complete symptom remission. Alternatively, individuals with more education may also have greater financial resources that allow them to get services and support that help with BD recovery outcomes. It must be noted that while there was a lot of heterogeneity by site in educational attainment in this global sample, overall this was a relatively well-educated sample with an average of at least a high school education (mean years of education 13.2, SD 3.8) and findings may not be generalizable to groups with lower educational attainment.

An important caveat to interpreting the results of these analyses is the fact that our characterization of mixity was derived from scores on standardized symptom rating scales for mania and for depression. There is not clear consensus on what might constitute mixity among OABD, particularly with respect to thresholds on the YMRS, MADRS and HAM-D. A 2005 study by Suppes and colleagues in mixed age adults and based on DSM IV-TR criteria which required the full constellation of manic/hypomanic and depressive symptoms concurrently, classified mixed cases as having a total YMRS score of 12 or higher and an

Inventory of Depressive Symptomatology–Clinician-Rated Version score of 15 or higher (22). More conservative values might be applied if one considers the goal to be BD remission. Tohen et al. (23) defined BD mania remission as a total score of < 5 and Berk et al. (24) noted that a YMRS score < 4 approximates remission. A 2009 International Society of Bipolar Disorder (ISBD) consensus summary of recommendations on remission using rating scales suggests a threshold of 5 or 7 on the HAM-D and a threshold of 4 or 7 on the YMRS (16). Given the broadened eligibility for mixed features (3 symptoms on either pole in DSM-5), the fact that most of the GAGE-BD sample are outpatients not in acute affective episodes, and the observation that the GAGE-BD sample skews towards lower manic symptoms, our classifications of mixity seems appropriate for our specific sample, but may not necessarily generalize to the larger population with OABD.

This study had a number of additional limitations inherent in an analysis of archival data and use of an aggregated sample from diverse sources. Meta-data were heterogeneous, and although none of the original studies focused on mixed states, the fact that some studies had inclusion criteria that specifically included variables relevant to symptom severity (COG-BD, UPMC, GERI SAD studies) could have led to enrichment of certain subgroups in these samples. Depressive symptoms were assessed using different evaluation methods and harmonization procedures to facilitate data analysis resulted in a loss of information granularity as continuous measures were collapsed into broad or selective categories. The cross-sectional design also limits interpretation because the duration and stability of the pattern of relative symptom severity captured at one baseline visit is unknown, and one cannot evaluate potential causal effects of mixed features of OABD on function when they are measured concurrently. A prospective, longitudinal and homogeneous cohort design would have likely delivered stronger conclusions about causality (25). Finally, the overall GAGE-BD sample had fairly low severity of both mania and depression symptoms, were generally outpatients, and most had a typical age of onset in early adulthood, so our estimates of the prevalence of the mixity subgroups may not generalize to OABD with more severe or acute symptoms or those with a late onset of the disorder.

In conclusion, these analyses of different OABD groups with mixed versus unipolar versus absent BD symptoms suggests that mixity to some degree is very common in this age group, with about 16% showing concurrent high severity of mania and depression. Mixity is associated with greater functional impairment; those with mixity characterized by higher depression severity have particularly impaired functioning. Given that treatment of mixed symptoms and bipolar depression is challenging, and very few clinical trials of any sort exist for OABD, more work is needed to determine the best approaches to maximize functioning and promote recovery in people with BD as they age. In addition, future studies to investigate whether mixed symptoms could contribute to functional decline in OABD should include cognitive and other biological variables, as well as employ longitudinal designs that will allow for better evaluation of causal effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding & Acknowledgements:

This project was supported by the International Society for Bipolar Disorders (ISBD) Bowden Massey Strategic Research Initiative; US National Institute of Mental Health (R01MH070902, R01MH113230, R01MH084921); Pfizer; Glaxo Smith Kline; Merck; National Health and Medical Research Council of Australia; National Institute for Biomarker Research in Neuropsychiatry, INBION (FAPESP 14/50873-3; 2016/01302-9 and CNPq 465412/2014-9); Associação Beneficente Alzira Denise Hertzog da Silva (ABADHS); Canadian Institutes for Health Research, grant 200017; Ministry of Science and Technology, Taiwan; Spanish Ministry of Science and Innovation (PI15/00283, PI18/00805) integrated into the Plan Nacional de I+D+I and co-financed by the ISCIII-Subdirección General de Evaluación and the Fondo Europeo de Desarrollo Regional (FEDER); the Instituto de Salud Carlos III; the CIBER of Mental Health (CIBERSAM); the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017 SGR 1365); the CERCA Programme; and the Departament de Salut de la Generalitat de Catalunya for the PERIS grant SLT006/17/00357.

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The authors would like to thank the following people: Daniel M. Blumberger, Lejla Colic PhD, James Emanuel, Leon Flicker, Jonathan Golledge, Graeme J. Hankey, Tokie Kemp, Nicole Korten, Beny Lafer, Patrick Monette, Laura Montejo, Melis Orhan, Susan Quatrano, Tarek K. Rajji, Miranda Skurla, Luca Villa PhD, and Bu B. Yeap.

Disclosures/Conflicts of Interest:

LTE received funding for this project from the International Society for Bipolar Disorders (ISBD) Bowden Massey Strategic Research Initiative to her institution as a subcontract and from the National Institutes of Health (NIH) (grant R01MH113230) to her institution for collection of data contributed to the analysis in the manuscript. She also receives direct salary support from the VA Desert-Pacific Mental Illness Research Education and Clinical Center.

FBSB has received grants from the National Institute of Nursing Research (NINR), the National Institute of Neurological Disorders and Stroke (NINDS), and the Michael J. Fox Foundation through his institution for various psychiatry research projects unrelated to the current manuscript.

SR has received a salary award from the Fonds de Recherche Quebec- Sante, and has shares in Aifred Health.

OPA has received competitive project grant funding from National Health and Medical Research Council of Australia (NHMRC) (1060557 and 1150529) for various psychiatry research projects unrelated to the current manuscript.

HPB received funding for this project from the NIH (grants R01MH070902 and R01MH113230).

BPF has received grant support from the National Institute on Aging (NIA) through Biogen, the Rogers Family Foundation through Eli Lily, and the Spier Family Foundation through Eisai for various psychiatry research projects unrelated to the current manuscript. He also receives consulting fees from Biogen and Acadia Pharmaceuticals, and is the President of the American Association for Geriatric Psychiatry.

REP has received grant support as co-I or key personnel from the NIA and the Rogers Family Foundation for various geriatric psychiatry research projects unrelated to the current manuscript. He has received partial salary support from Biogen and Eisai for work on industry-sponsored Alzheimer's clinical trials, also unrelated to the current manuscript.

OVF has received payments from Biogen for participation in an advisory board and creation of educational information. He receives regularly delivered samples of approved medications and publicity material from several pharmaceutical companies, according to Brazilian regulations.

AG has received funding from the NIH (grant R01AG055389), the NIA (grant P30AG066468), the National Cancer Institute (grant R01CA149105), and the National Heart, Lung, and Blood Institute (NHLBI) (grant R01HL131531) for various psychiatry research projects unrelated to the current manuscript. She is also a participant in advisory and monitoring boards for studies NCT02674529 and NCT03128021.

EJ received funding support for this project from the Spanish Ministry of Science and Innovation (grants PI15/00283 and PI18/00805) integrated into the Plan Nacional de I+D+I and co-financed by the ISCIII-Subdirección General de Evaluación and the Fondo Europeo de Desarrollo Regional (FEDER); the Instituto de Salud Carlos III; the CIBER of Mental Health (CIBERSAM); the Secretaria d'Universitats i Recerca del

Departament d'Economia i Coneixement (2017 SGR 1365); the CERCA Programme; and the Departament de Salut de la Generalitat de Catalunya for the PERIS (grant SLT006/17/00357).

EV has received funding from Boehringer-Ingelheim, Janssen, and Novartis for various psychiatry research projects unrelated to the current manuscript. He is a consultant to Abbvie, Angelini, Biogen, GH Research, Janssen, Lundbeck, Richter, and Takeda. He has also received compensation for educational presentations from AB-Biotics, Angelini, Janssen, Lundbeck, Sunovion, and Takeda. He is a participant on advisory and monitoring boards at Glaxco-Smith-Klein, Janssen, Lundbeck, Otsuka, Sanofi-Aventis, and Sumimoto.

BM received funding support for this project from the Labatt Family Chair in Depression Biology in Late-Life adults through his institution and has received direct compensation from the Centre for Addiction and Mental Health (CAMH). He has received funding from Brain Canada, the Canadian Institutes of Health Research, the CAMH Foundation, the Patient-Centred Outcomes Research Institute, and the NIH for various psychiatry research projects unrelated to the current manuscript. He is an unpaid consultant for Myriad Neuroscience and holds a leadership role on the CAMH Board of Trustees. He has received honoraria from the: California Psychological Association; University of Texas Health (Houston); Beijing Anding Hospital - Capital Medical University; Shanghai Mental Health Center; Brain Hospital of Guangzhou Medical University; Houston Mood Disorders Conference UTHealth; L'AMPQ - Formation en gérontopsychiatrie; and UMass Psychiatry Grand Rounds. He has received software from Capital Solutions Design LLC and HAPPYneuron for clinical trials funded by the CAMH Foundation and Brain Canada respectively.

MS has research grants from Otsuka, Alkermes, Nuromate, the International Society of Bipolar Disorders (ISBD), NIH, and the Centers for Disease Control and Prevention (CDC). She is a consultant to Alkermes, Otsuka, Janssen, Neurocrine, Bracket, Health Analytics and Frontline Medical Communications and has received publication royalties from Springer Press, Johns Hopkins University Press, Oxford Press, UpToDate. She has received compensation for preparation of CME activities for: American Physician's Institute, MCM Education, CMEology, Potomac Center for Medical Education, Global Medical Education, Creative Educational Concepts, and Psychopharmacology Institute. Lastly, she has unpaid leadership positions on the Epilepsy Association Professional Advisory Board and the Depression and Bipolar Support Alliance (DBSA).

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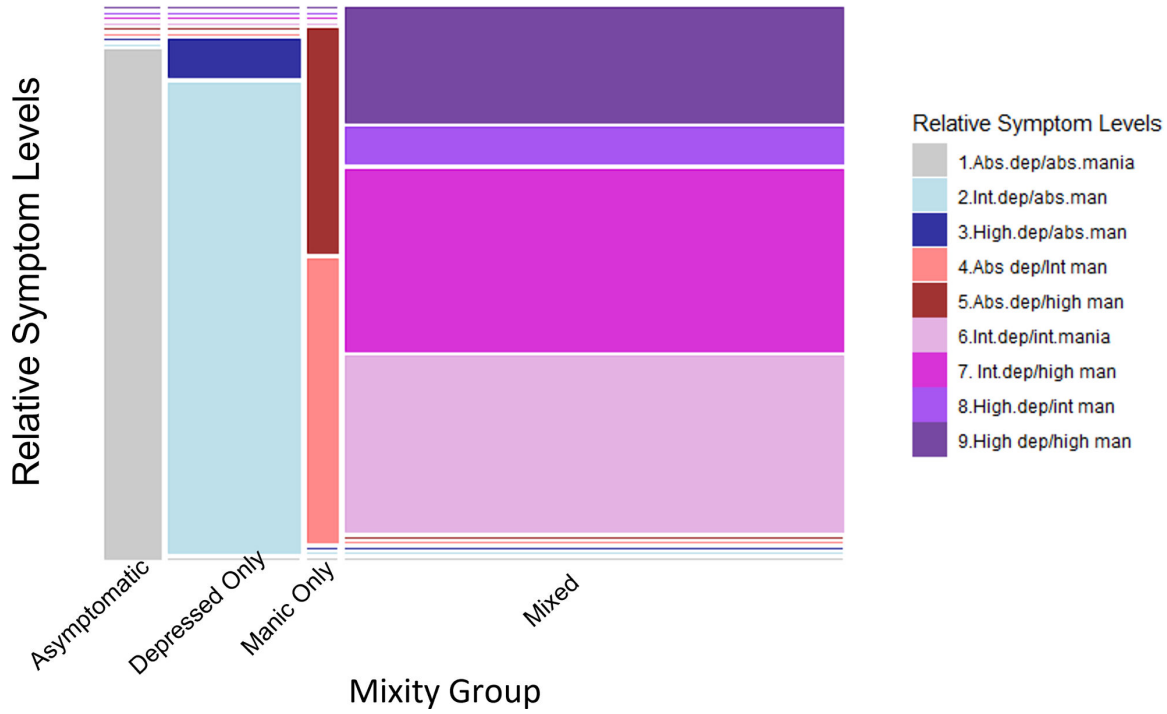

Figure 1:

Mosaic plot of the frequency of mixity groups and the composition of each mixity group in terms of relative symptom severity. The width of each box reflects the proportion of each mixity group within the total sample and the height of each box reflects the proportion of each relative symptom severity group within each mixity group. The area of the boxes reflects the proportion of the combinations of mixity group and symptom severity levels in the total sample. Gray color indicates asymptomatic participants (absent depression and absent mania); blue colors indicate the depressed only group: light blue indicates intermediate depression and absent mania and dark blue indicates higher depression and absent mania; red colors indicate the mania only group: light red indicates intermediate mania and absent depression; dark red indicates higher mania and absent depression; purple colors indicate the mixed group: light purple indicates intermediate depression and intermediate mania; reddish purple indicates intermediate depression and higher mania; blueish purple indicates high depression and intermediate mania; dark purple indicates higher depression and higher mania.

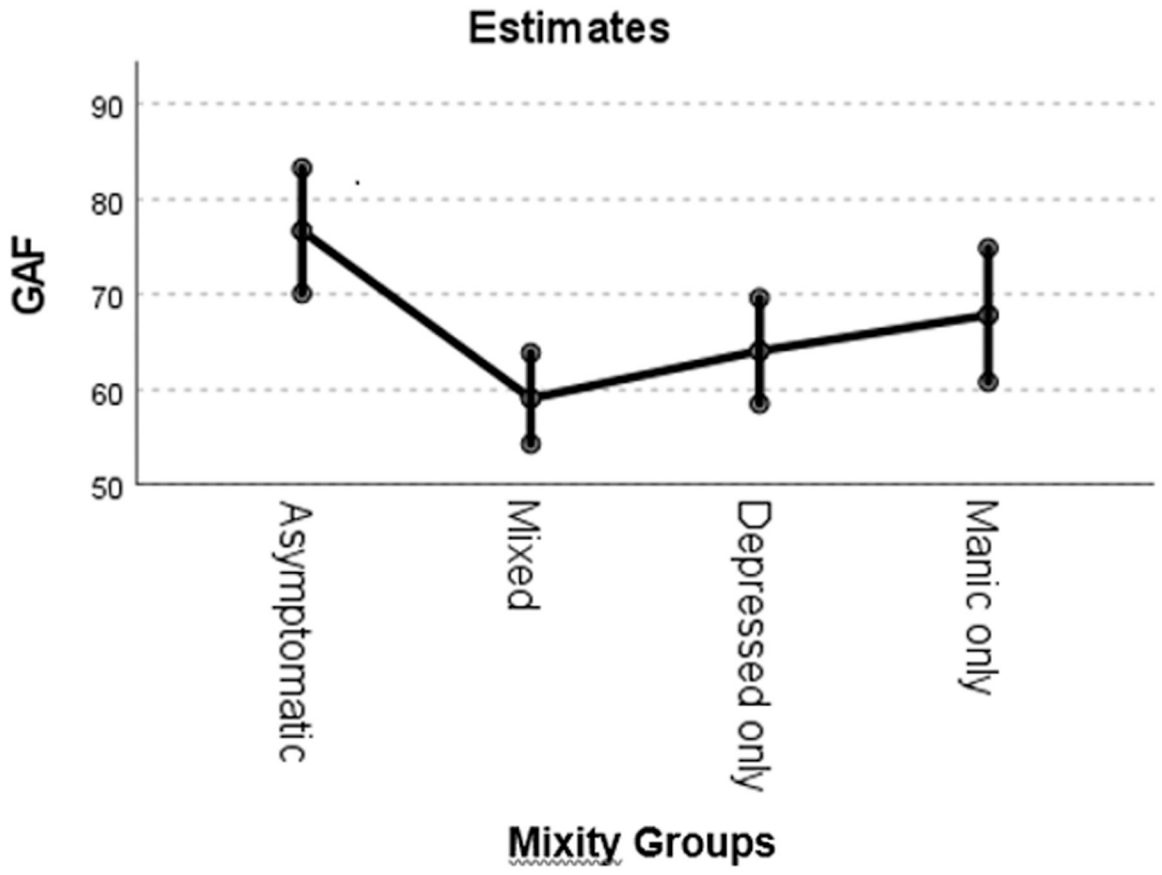

Figure 2:
Estimated marginal means for global assessment of functioning (GAF) scores for mixity groups from generalized linear mixed model that included site as a random intercept.

Table 1.

Total sample and mixity group characteristics and differences

	Total sample		Asymptomatic		Mixed		Depression Only		Mania Only		Group Difference[1]
	N	Mean (SD) or % (N)	N	Mean (SD) or % (N)	N	Mean (SD) or % (N)	N	Mean (SD) or % (N)	N	Mean (SD) or % (N)	F [DF], p
Age (in years)	804	56.8 (11.4)	63	61.8 (7.8)	559	55.3 (11.9)	148	59.5 (9.5)	34	60.5 (10.5)	F[3,800]=.339, p=.80
Gender (% female)	804	58.7% (472)	63	61.9% (39)	559	58.9% (329)	148	55.4% (82)	34	64.7% (22)	F[3,800]=.23, p=.87
Education (in years)	662	13.2 (3.8)	56	12.0 (5.4)	466	13.4 (3.4)	113	13.4 (3.9)	27	11.2 (5.5)	**F[3,658]=3.6, p=.014**
Employment (% currently working)	568	26.8% (152)	20	40.0% (8)	426	23.7% (101)	106	35.8% (38)	16	31.3% (5)	F[3,564]=.32, p=.81
BD subtype (% Type I)	734	75.2% (552)	36	72.2% (26)	537	73.9% (397)	138	79.7% (110)	23	82.6% (19)	F[3,674]=.191, p=.90
Age of onset (in years)	650	27.6 (14.2)	58	35.7 (14.2)	442	25.8 (13.9)	121	28.9 (13.1)	29	34.5 (15.0)	F[3,646]=.94, p=.42
Mania severity (YMRS) *	805	4.8 (5.4)	63	0.0 (0.0)	560	6.6 (5.2)	148	0.0 (0.0)	34	6.5 (6.2)	F[1,592]=.066, p=.80
Depression 3-level											F[6,797]=.819, p=.55
Depression group (% Lower)	805	66.0% (531)	63	0.0% (0)	560	70.4% (394)	148	92.6% (137)	34	0.0% (0)	--
Depression group (% Higher)	805	22% (177)	63	0.0% (0)	560	29.6% (166)	148	7.4% (11)	34	0.0% (0)	--
GAF	439	61.1 (12.8)	30	79.7 (11.2)	343	58.7 (11.5)	48	63.1 (12.7)	18	70.1 (9.6)	**F[3,435]=16.1, p=<0.001**

Note: BD=bipolar disorder; YMRS= Young Mania Rating Scale Score; GAF= Global Assessment of Functioning; bold indicates significant at P< .05

[1] Model included study cohort as a random intercept

* Total mean YMRS score

Table 2:

Most common symptom domains among OABD with high levels of manic symptoms + high levels of depressive symptoms (n=126). The count and percent of participants with data on individual items whose score was greater than zero on each item is given.

YMRS items (count, %) N=120	MADRS items (count, %) N=104	HAM-D items (count, %) N=38
7 – Language / thought disorder (111, 92.5%)	6 – Concentration difficulties (103, 99%)	1 – Depressed mood (37, 97.4%)
5 – Irritability (106, 88.3%)	3 – Inner tension (100, 96.2%)	10 – Psychic anxiety (37, 97.4%)
4 – Reduced sleep (100, 83.3%)	1 – Apparent sadness (99, 95.2%)	11 – Somatic anxiety (37, 97.4%)
6 – Rapid speech (47, 39.2%)	2 – Reported sadness (99, 95.2%)	7 – Work and activities (36, 94.7%)
9 – Disruptive / aggressive behavior (46, 38.3%)	4 – Reduced sleep (98, 94.2%)	2 – Guilt (32, 84.2%)