Title

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Journal

American Journal of Geriatric Psychiatry, 27(10)

ISSN

1064-7481

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Publication Date

2019-10-01

DOI

10.1016/j.jagp.2019.04.003

Peer reviewed

HHS Public Access

Author manuscript

Am J Geriatr Psychiatry. Author manuscript; available in PMC 2020 October 01.

Published in final edited form as:

Am J Geriatr Psychiatry. 2019 October ; 27(10): 1122–1134. doi:10.1016/j.jagp.2019.04.003.

Understanding Aging in Bipolar Disorder by Integrating Archival Clinical Research Datasets

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Abstract

While 25% of people with bipolar disorder (BD) are over age 60, there is a dearth of research on older age bipolar disorder (OABD). This report describes an initial effort to create an integrated OABD database using the U.S. National Institute of Mental Health Data Archive (NDA). Goals were to: 1) combine data from 3 U.S. BD studies that included overlapping data elements, 2) investigate research questions related to aims of the original studies, and 3) take an important first step toward combining existing datasets relevant to aging and BD.

Data were prepared and uploaded to the NDA, with a focus on data elements common to all studies. As appropriate, data were harmonized to select or collapse categories suitable for cross-

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walk analysis. Associations between age, BD symptoms, functioning, medication load, medication adherence and medical co-morbidities were assessed.

The total sample comprised 451 individuals, mean age 57.7 (SD 13.1). Medical comorbidity was not significantly associated with either age or functioning and there did not appear to be an association between medication load, comorbidity, age and adherence. Men and African-Americans were significantly more likely to have poor adherence. Both BD mania and depression symptoms were associated with functioning, but this differed across studies. In spite of limitations including heterogeneity in study design and samples and cross-sectional methodology, integrated datasets represent an opportunity to better understand how aging may impact the presentation and evolution of chronic mental health disorders across the life-span.

Keywords

bipolar disorder; geriatric; harmonization; medication adherence; functioning

Introduction:

While 25% of BD patients are over 60 years old (1), research on older age bipolar disorder (OABD) is limited. The International Society for Bipolar Disorders (ISBD) convened a global panel that summarized the existing evidence base on OABD (2), and noted many important gaps such as a clear understanding of mood symptom evolution and medical comorbidity characterization.

One way to maximize output from limited available studies is to share data to bring the combined power of rigorous studies to bear on crucial questions in BD and aging. Due to the clinical heterogeneity of OABD, large samples will be needed to find subgroups or clusters of trajectories and risk factors. This report describes a recent U.S. National Institute of Mental Health (NIMH) funded project to create an integrated OABD database using the resources of the NIMH Data Archive (NDA), the Aging & Geriatric Experiments in Bipolar Disorder Database (AGE-BD). Goals of the AGE-BD were to: 1) combine data from 3 U.S. BD studies that included overlapping data elements, 2) investigate research questions related to the original aims of the studies, and 3) take an important first step toward combining existing datasets relevant to aging and BD by creating a template for harmonizing data across investigations. As a proof of concept, we tested several hypotheses about the shared variables relevant to OABD. We hypothesized that older BD patients would have greater medical burden and that medical burden would be associated with lower functioning. We further expected that poor medication adherence would be more common among patients on more medications and with greater medical burden. We also expected that more severe BD symptoms would be associated with lower functioning and explored associations between demographic variables, BD symptoms, functioning, and physical health.

Methods:

We combined and analyzed available measures from 3 NIMH-funded BD studies. Table 1 illustrates demographic and clinical characteristics of the study sample. A brief description of the study design for each of the contributing datasets follows.

Contributing Studies

University of California San Diego (UCSD) study: The aim of this ongoing longitudinal study of outpatients is to compare trajectories of cognitive aging between those with and without BD and to identify predictors of short-term and long-term cognitive change. The study uses an accelerated longitudinal burst design in which participants of various ages and are studied in two-week “burst” assessments of clinical, cognitive, and medical variables at week 0, 1, and 2, as well as ecological momentary assessment via smartphone and actigraphy. Inclusion criteria are DSM-IV diagnosis of bipolar I or II, age 25–60 years, currently outpatient, proficient in English, and capable of giving informed consent; exclusion criteria are acute medical illness or chronic pain necessitating medication, recent vaccination, history of neurological disorder or loss of consciousness greater than 15 minutes, history of radiation or chemotherapy treatment, uncontrolled diabetes or hypertension, sensory limitations precluding cognitive testing, or having a court- designated decision maker. For this analysis, only assessments from BD patients in the first year of the longitudinal study were used.

Case Western Reserve University (CWRU) study: This 6-month, prospective randomized controlled trial enrolled 184 poorly adherent BD patients randomized to a customized adherence enhancement (CAE, N=92) vs. educational control (EDU, N=92) (3). Study inclusion criteria were either type I or type II BD as confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID),(4) BD for at least 2 years, prescribed BD medication for at least 6 months and ≥ 20% non-adherent as assessed by the Tablets Routine Questionnaire (TRQ) for an “index” BD drug (5).

Acute Pharmacotherapy of Late-Life Mania (GERI-BD) study: The GERI-BD study was a 9-week, double-blind, randomized trial of divalproex vs. lithium for acute Type 1 BD mania in adults age ≥ 60 years (6). Participants had a current manic, mixed, or hypomanic episode(7) based on the SCID (8); and Young Mania Rating Scale (YMRS) (9, 10) score ≥ 18 Patients were excluded if they had contraindication to lithium or divalproex, an unstable medical condition, dementia or active substance dependence. Baseline assessments prior to starting study drug, were used for this analysis. We considered inpatients and outpatients separately since both the CWRU and UCSD samples were only outpatients.

Data in the AGE-BD sample did not include any individual identifiers or personal health information (PHI). The analysis of the pooled de-identified CWRU and UCSD data was approved by the local Institutional Review Boards (IRBs). Downloading of NIMH Data Archive data was conducted in accordance with a data use certification (DUC) between the CWRU and UCSD sites and NIMH.

Data preparation, Measures, Data harmonization

The UCSD and CWRU data were prepared and uploaded to the NDA; GERI-BD data were already available in NDA. The procedures used to prepare and upload the files are described in a supplemental on-line appendix (Supplemental Methods). Following these efforts, SPSS scripts were written to merge the data into a comprehensive analytical file.

The UCSD and CWRU studies both used the Brief Psychiatric Rating Scale (BPRS) (11) to assess global psychopathology. All 3 studies used the Young Mania Rating Scale (YMRS) (10) to assess manic symptoms and the Global Assessment of Functioning (GAF) (12) for functional status evaluation.

Additional harmonization was necessary for several data elements including depression severity, medical comorbidity, and medication adherence. For depression severity, the instruments harmonized were the Hamilton Depression Scale (HAM-D)(13) used by UCSD and GERI-BD, and the Montgomery-Asberg Depression Scale (MADRS)(14) used by CWRU. For medical comorbidity, harmonization was conducted for an in-house medical history questionnaire (an adapted version of the CIRS-G) used by UCSD, the self-rated Charlson Comorbidity Index used by CWRU (15), and Cumulative Illness Rating Scale for Geriatrics (CIRS-G) used by GERI-BD (16, 17). Medication adherence was harmonized across daily medication adherence ratings (through smartphone survey) used by UCSD, Tablets Routine Questionnaire (TRQ) used by CWRU, and weekly categorical adherence ratings used by GERIBD.

Depression was harmonized by creating a Depression Rating score, with a value range of 0 to 4; 0=No depression, 1=Mild depression, 2=Moderate depression, 4=Severe depression. Cutoffs used for the HAM-D were no depression (0–7); mild depression (8–16); moderate depression (17–23); and severe depression (≥24) (18). While there have been various suggestions on how to cross-walk the MADRS with other symptom severity measures (19, 20), for this analysis, cutoffs used for the MADRS were no depression (0–6); mild depression (7–19); moderate depression (20–34); and severe depression (≥35) (21–23).

Medical comorbidity from the detailed medical history taken by UCSD, Charlson Comorbidity Index used by CWRU, and CIRS-G used by GERI-BD, was harmonized to five categories. Individual variables were calculated for each category identifying whether the subject had positively endorsed having been diagnosed for a condition within the category or not, as well as the total number of categories endorsed.

Medication adherence was harmonized by creating an Adherence Rating, consisting of three categories: good adherence, moderate adherence, and poor/non-adherence. UCSD tracked daily adherence from baseline over 14 days, which asked participants if they took all, some, or none of their medications. Responses were grouped together into the week for which they occurred (week 1 or week 2). Weeks for which at least four responses were received were included and a weekly adherence rating was calculated: good adherence (≥80% days took all medications), moderate adherence (50–79% days took all medications), poor/non-adherence (<50 % days took all medications).

CWRU assessed adherence using the TRQ at screening, baseline, and 3 additional follow-up points. An adherence rating was calculated for each visit: good adherence (<20% of medications missed), moderate adherence (20–50% of medications missed), poor/non-adherence (>50% of medications missed). Only screening and baseline measures were used in this analysis.

GERI-BD did not track baseline adherence, but did measure adherence during the clinical trial at various time-points. We chose the Day 4 visit as most comparable to the week 1 / screening visits and Day 15 as most comparable to the week 2/baseline visits of the other two studies. Adherence ratings derived from medication logs based on patient input/clinical assessment. Good adherence was indicated by a score of 1 (took medication 81–100% of the time), 10 (Adequate adherence: May forget to take medications up to one day per week or no more that 15% to 20% of weekly doses) or 11 (Takes all medicines or forgets occasional doses). Moderate adherence was indicated by a score of 2 (took medication 61–80% of the time), 3 (took medication 41–60% of the time), 8 (Takes medications about half of the time), or 9 (Takes medicines about 2/3 of the time). Poor adherence was indicated by a score of 4 (Takes medication 21–40% of the time), 5 (Takes medication 0–20% of the time), 6 (Has not taken medications), or 7 (Only occasionally takes medicines).

Data Analysis:

We compared measures between the samples using ANOVA and Tukey's Honestly Significant Difference for pairwise comparisons for continuous measures and χ^2 for discrete measures. Given substantial sample differences, we adjusted for sample in all subsequent analyses. We then examined the inter-relationship of age and functioning with medical comorbidities using a multinomial logistic regression. Binomial logistic regression examined the relationship of medication burden and medical comorbidities to adherence subgroups. For exploratory analyses, we used χ^2 for analyses with discrete predictors and dependent variables. For continuous variables, normality assumptions were assessed. Analyses with both continuous predictors and dependent variables were conducted with general linear models. For analyses with discrete variables as predictors, ANCOVA was used (with sample as covariate).

Results:

Overall Study Sample

The total combined sample was 451 individuals, mean age 57.7 (SD 13.1) with the subsamples from UCSD, CWRU, and the outpatients and inpatients from GERI-BD being different in many respects (Table 1). The only variables *without* significant sub-sample differences were the proportion of subjects with respiratory, renal, and liver conditions, and the number of lifetime psychiatric hospitalizations and BPRS.

The GERI-BD sample was older, had more severe mania, greater medical comorbidity, more psychotropic and non-psychotropic medications, and poorer functioning compared to the other 2 samples. There were also fewer woman and depression scores were lower. The GERIBD inpatient and outpatient samples differed significantly on some measures including

that inpatients had lower functioning, higher mania severity, and were taking more psychotropic and total medications. To enhance comparability, further analysis of the GERI-BD sample included only outpatients.

The CWRU sample also had some unique characteristics, having the largest proportion of African Americans, least formal education (although the average was greater than 12 years for all samples), more smokers, higher body mass index (BMI), and the only study with Bipolar II participants. The sample contained a much higher proportion of poor and moderately adherence patients compared to the other samples (Figure 1). For some variables, all 3 sites were significantly different from one another. Age of onset was oldest in GERI-BD sample, intermediate in CWRU, and youngest in the UCSD sample. Hispanic ethnicity was most prevalent in UCSD, intermediate in GERI-BD, and least common in the CWRU sample. We controlled for sample in all analyses.

Medical burden, age, and functioning

Total and categorical medical comorbidity burden were not significantly associated with either age or functioning (Supplemental Table 1).

Medication adherence

When comparing those with good and moderate adherence to those with poor adherence in the first week of each study (Visit 1/Day 4) while controlling for sample, there were no relationships with age, sex, race, mania severity, depression severity score, total number of medical conditions, or the total number of current medications taken. However, when examining adherence about a week later (Visit 2 / Day 15), there was a significant relationship with gender such that men were more likely to be poorly adherent (odds ratio [OR] (confidence interval) = 2.5 (1.35,4.65)). In addition, African-Americans were more likely to be poorly adherent (OR = 2.0 (1.05, 3.81).

Mood symptoms and functioning

Individuals with more severe mania had poorer functioning as measured by the GAF ($F(1,331) = 23.8$, $p < 0.0001$, $\eta^2_{partial} = .07$; Figure 2a). When a sample x mania symptom term was added to the model, there were significant main effects of sample ($F(1,330) = 5.8$, $p=0.02$, $\eta^2_{partial} = .017$) and mania severity ($F(1,330) = 7.2$, $p = 0.01$, $\eta^2_{partial} = .02$), and a significant interaction ($F(1,330) = 6.4$, $p = 0.01$, $\eta^2_{partial} = .02$) . As illustrated in Figure 2a, greater manic symptoms were associated with poorer functioning scores in the CWRU and GERI-BD outpatient samples, but not in the UCSD sample. Functioning was associated with depression severity, as well ($F(3,329) = 19.0$, $p<0.0001$, $\eta^2_{partial} = .15$), in the context of a strong main effect of sample ($F(1,329) =70.3$, $p<0.0001$, $\eta^2_{partial} = .18$). When a sample x depression score interaction was added to the model, the main effects remained significant and there was a significant interaction as well ($F(3,326) = 10.9$, $p < 0.0001$, $\eta^2_{partial} = .09$). As seen in Figure 2b, worse depression was associated with worse functioning in the CWRU and UCSD, but not GERI-BD outpatient sample.

Exploratory relationships among variables

We examined demographic (age, gender, education, race) and health-related (smoking, BMI) correlates of mood severity and functioning after controlling for sample. Depression severity was higher among women (OR = .70 (.53,.93); Figure 3), but there were no other significant demographic correlates of depression severity, nor were smoking or BMI associated. Mania severity was not different by age, gender, education, or race and did not relate to smoking or BMI. As seen in Figure 4 and 5 respectively, GAF was lower among those with less education (F (1,331) = 8.0, p=0.005, $\eta^2_{partial}$ = .02) and among smokers (F (1,301) = 4.6, p=0.03, $\eta^2_{partial}$ = .02), but no other associations were significant.

For physical health related variables, older individuals (F (1, 278) = 4.04, p=0.04, $\eta^2_{partial}$ = .014), men (F(1,278)=6.16, p=.01, $\eta^2_{partial}$ = .022), Caucasians (F(1,262)=3.9, p=0.05, $\eta^2_{partial}$ =.015) and those with fewer medical conditions (F(1,255)=2.7, p=0.02, $\eta^2_{partial}$ = .053) had lower BMI across the samples. Smokers were less educated (F(1,302)=17.5, p<.0001, $\eta^2_{partial}$ = .055) and more likely to be African American than Caucasian (OR = 2.5 (1.5,4.3)) . There were no significant demographic correlates of number of medical conditions or total medication burden.

Discussion:

This analysis combining datasets of varying age individuals with BD illustrates the potential utility of an integrated database to examine issues related to aging and various domains of health and functional outcome. As expected for an analysis of archival data from studies with disparate inclusion criteria, aims and designs, the samples differed with respect to demographic and clinical variables. Additionally, some of the domains of interest, such as depressive symptoms and adherence were assessed using different instruments. Harmonization procedures to facilitate cross-walk analysis resulted in some loss of granularity as continuous measures were collapsed into broad or selective categories. In spite of these limitations, aggregate analyses can provide insights into how aging, BD symptoms, medical burden and functioning inter-relate and allow investigators to examine associations between clinical variables that might not be possible given sample size limitations in individual studies. Additionally, this analysis took advantage of the U.S. NIMH Data Archive, a publicly available resource that includes data from well-defined samples in clinical research studies.

While most individuals were overweight or obese, the AGE-BD sample endorsed an average of 1–2 medical conditions, primarily, heart disease and respiratory conditions. In contrast to our initial hypothesis, we did not find an association between age, medical burden and functioning. Possibly the process of data harmonization could have obscured a significant link between medical burden and age. Alternatively, individuals enrolled in research may be a particularly healthy sample that is not necessarily representative of the broader population of people with BD. Other literature reports suggest that OABD patients have an average of 3 to 4 comorbid medical conditions, including metabolic syndrome (up to 50%), hypertension (4569%), diabetes mellitus (18–31%), cardiovascular disease (9–49%), respiratory illness (4–15 %), arthritis (16–21%), endocrine abnormalities (17–22%), as well as atopic diseases such as allergic rhinitis and asthma (6–20%) (24, 25). Co- morbidities associated with

OABD are also evident throughout the lifespan including in youth and younger adults with BD (26, 27).

Individuals in this sample were prescribed multiple medications for both BD and for medical conditions. As expected, older BD patients were prescribed more drugs for medical conditions (an average of 4–5 drugs in the GERI-BD outpatient sample and an average of 5–6 drugs in the inpatient sample). In the studies that did not restrict or determine medication prescribing (CWRU and UCSD samples), individuals were prescribed an average of 2–3 BD medications. Contrary to our original expectations, we did not find a relationship between medication load, medical burden and adherence, and older age was not associated with adherence level. Poor adherence is common in people with BD (28), but accurate assessment is challenging, especially when relying upon self-report methods. Consistent with other reports, which have identified gender and minority status as predictors of sub-optimal adherence,(28) we found that men and African-Americans were significantly more likely to have poor adherence.

As a final preliminary hypothesis, we expected that more BD symptoms would be associated with worse functioning and did in fact find this relationship, although the findings suggest a somewhat nuanced association between symptoms and functioning related to mood polarity. More severe manic symptoms were associated with worse functioning in the samples with acute mania (GERI –BD study) and the sample with poor adherence (CWRU) but not with the sample that did not specifically enroll individuals who were highly symptomatic or poorly adherent (UCSD). More severe depression was associated with worse functioning in the sample with poor adherence (who were mostly depressed) and in the sample that did not target individuals who were highly symptomatic or poorly adherent (UCSD). These findings are consistent with the review by Gitlin and Miklowitz (29), which found evidence for some association of functional outcome with manic symptoms, but a particularly strong relationship to depressive symptoms, even at a sub-syndromal level.

An important caveat to interpretation of functional status results in this combined sample is that it does not include individuals with substantial cognitive impairment. Individuals with dementia were specifically excluded from the GERI-BD study and individuals who might have difficulty providing informed consent due to cognitive impairment would have been excluded from any of the 3 studies. There have been few long-term studies on the association between BD and cognitive functioning.(30–33) Some reports note a positive association between BD and cognitive worsening over time.(30–33) In order to clarify the trajectory of functioning in OABD, cognitive assessments will need to be included and considered in the context of BD symptoms and illness progression.

This integrated dataset highlights some of the strengths and challenges of using integrated and publicly available data. The NDA infrastructure includes on-line and in-person support, a wealth of data, and links to publications derived from uploaded data. Limitations include heterogeneity in the types of supporting documentation needed to understand the context of specific studies and effort involved in aggregating, harmonizing and analyzing the data. While researchers can access publications that describe the study design and how variables were collected, the documentation is inconsistent and it is difficult to ascertain meta-data

variables such as how the research sample might compare to the broad population of individuals with a given health condition. As more data is contributed to NDA, it likely will provide a more complete picture of how chronic conditions like BD may evolve over time. Recently, NDA has announced a new Data Exploration and Analysis Portal (DEAP) that may provide some analytic support (34). Additionally, with the support of ISBD, an international team of scientists has begun expansion of AGE-BD to include global datasets and new analyses specific to OABD.(35)

An important consideration, even in our relatively limited sample, is sample interaction effects. For several of our analyses, we found that associations between variables differed depending on the sample, likely due to meta-data differences between studies. Meta-data variables such as specific study inclusion/exclusion criteria, where/when a study was conducted and research design issues such as whether a study featured an intervention vs. observation have the potential to affect multiple outcomes. Future analyses strategies need to consider these metadata variables in addition to subject-level variables and should include interaction terms in the models if sample effects are present.

This study had a number of limitations including limited sample size, differing study designs and samples, and reliance on cross-sectional data. While quantitative assessments in each study were done by a single rater trained by the study PIs to pre-established and documented reliability standards, there is no way to determine that training and reliability of measures across studies were equivalent. In spite of these limitations, findings provide a possible template to overcome some of the existing challenges to being able to study the important issue of aging and BD.

Our relatively small study and related analyses do not provide findings that will transform our field, and the promise of pooled datasets remains to be established. However, our experience has potential to pave the way for a process of aggregate data analysis, whether sample findings are pooled or analyzed separately but in a coordinated way, that may overcome some of the severe limitations that impede being able to better understand conditions that up until now have been studied mainly in small/isolated samples. Our global integrated dataset study (33), which builds upon the analysis presented here, involves over 15 international sites conducting research in OABD, with an expected OABD sample size of over 1,000 cases. Advantages of combining datasets are that it affords better estimates of effect sizes and larger/combined datasets may facilitate identification and characterization of sample sub-groups that can be a target of clinical focus. Taken together, an integrated dataset that builds upon models such as that presented here represents an opportunity to better understand how aging may impact the evolution of chronic mental health disorders across the life-span.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Conflicts of Interest:

Author LTE reports grants from NIMH during the conduct of the study. Authors MEA, RED, KH, CT, RCY and have nothing to disclose. Author MS reports grants from Otsuka, Merck, Alkermes, Janssen, Reuter Foundation, Woodruff Foundation, Reinberger Foundation, National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), personal fees from Bracket, Otsuka, Sunovion, Neurocrine, Supernus, Health Analytics, other from Springer Press, Johns Hopkins University Press, Oxford Press, UpToDate, other from American Physician's Institute, MCM Education, CMEology, Potomac Center for Medical Education, Global Medical Education, and Creative Educational Concepts during the conduct of the study.

References:

1. Sajatovic M, Blow FC, Ignacio RV, et al.: Age-related modifiers of clinical presentation and health service use among veterans with bipolar disorder. Psychiatr Serv 2004; 55:1014–1021 [PubMed: 15345761]
2. Sajatovic M, Strejilevich SA, Gildengers AG, et al.: A report on older-age bipolar disorder from the international society for bipolar disorders task force. Bipolar Disord 2015; 17:689–704 [PubMed: 26384588]
3. Sajatovic M, Tatsuoka C, Cassidy KA, et al.: A 6-month, prospective, randomized controlled trial of customized adherence enhancement versus bipolar-specific educational control in poorly adherent individuals with bipolar disorder. J Clin Psychiatry 2018; 79:
4. First MB, Spitzer RL,Gibbon M: Structured clinical interview for axis i dsm-vi disorders- (scid) patient edition, version 2.0, New York, NY: Biometrics Research Department, New York Pyschiatric Institute, 1996
5. Sajatovic M, Levin JB, Sams J, et al.: Symptom severity, self-reported adherence, and electronic pill monitoring in poorly adherent patients with bipolar disorder. Bipolar Disord 2015; 17:653–661 [PubMed: 26529124]
6. Young R, Mulsant B, Sajatovic M, et al.: A randomized double-blind controlled trial of lithium and divalproex in the treatment of mania in older patients with bipolar disorder. American Journal of Psychiatry In Press;
7. American Psychiatric Association: Diagnostic and statistical manual dsm-iv- tr, 4th ed. Washington, D.C, American Psychiatric Press, Inc, 1994
8. First MB, Spitzer R, Williams J, et al.: Structured clinical interview for dsm-iv patient version (scidp) American Psychiatric Press, Inc 1995;
9. Young RC, Biggs JT, Ziegler VE, et al.: A rating scale for mania: Reliability, validity, and sensitivity. British Journal of Psychiatry 1978; 133:429–435 [PubMed: 728692]
10. Young RC, Biggs JT, Ziegler VE, et al.: A rating scale for mania: Reliability, validity and sensitivity. Br J Psychiatry 1978; 133:429–435 [PubMed: 728692]
11. Overall JA,Gorham DR: The brief psychiatric rating scale. Psychological Reports 1962; 10:799–812
12. Spitzer RL, Gibbon M, Williams JBW, et al.: Global assessment of functioning (gaf) scale, in Outcome assessment in clinical practice Edited by Sederer LJ,Baltimore Dickey B., MD Williams and Wilkins, 1996, pp
13. Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62 [PubMed: 14399272]
14. Montgomery SA,Asberg M: A new depression scale designed to be sensitive to change. Br J Psychiatry 1979; 134:382–389 [PubMed: 444788]
15. Chaudhry S, Jin L,Meltzer D: Use of a self-report-generated charlson comorbidity index for predicting mortality. Med Care 2005; 43:607–615 [PubMed: 15908856]
16. Linn BS, Linn MW,Gurel L: Cumulative illness rating scale. J Am Geriatr Soc 1968; 16:622–626 [PubMed: 5646906]
17. Miller MD, Paradis CF, Houck PR, et al.: Rating chronic medical illness burden in geropsychiatric practice and research: Application of the cumulative illness rating scale. Psychiatry Res 1992; 41:237–248 [PubMed: 1594710]
18. Zimmerman M, Martinez JH, Young D, et al.: Severity classification on the hamilton depression rating scale. J Affect Disord 2013; 150:384–388 [PubMed: 23759278]

19. Leucht S, Fennema H, Engel RR, et al.: What does the madrs mean? Equipercentile linking with the cgi using a company database of mirtazapine studies. J Affect Disord 2017; 210:287–293 [PubMed: 28068617]
20. Leucht S, Fennema H, Engel RR, et al.: Translating the ham-d into the madrs and vice versa with equipercentile linking. J Affect Disord 2018; 226:326–331 [PubMed: 29031182]
21. Muller-Thomsen T, Arlt S, Mann U, et al.: Detecting depression in alzheimer's disease: Evaluation of four different scales. Arch Clin Neuropsychol 2005; 20:271–276 [PubMed: 15708735]
22. Herrmann N, Black SE, Lawrence J, et al.: The sunnybrook stroke study: A prospective study of depressive symptoms and functional outcome. Stroke 1998; 29:618–624 [PubMed: 9506602]
23. McDowell I: Montgomery-asberg depression rating scale (madrs) biopsychosocial assessment tools for the elderly- assessment summary sheet in Measuring health: A guide to rating scales and questionnaires London, Ontario, Canada, Oxford University Press, 2006, pp
24. Lala SV,Sajatovic M: Medical and psychiatric comorbidities among elderly individuals with bipolar disorder: A literature review. J Geriatr Psychiatry Neurol 2012; 25:20–25 [PubMed: 22467842]
25. Tsai SY, Kuo CJ, Chung KH, et al.: Cognitive dysfunction and medical morbidity in elderly outpatients with bipolar disorder. Am J Geriatr Psychiatry 2009; 17:1004–1011 [PubMed: 20104057]
26. Goldstein BI, Fagiolini A, Houck P, et al.: Cardiovascular disease and hypertension among adults with bipolar i disorder in the united states. Bipolar Disord 2009; 11:657–662 [PubMed: 19689508]
27. Hatch J, Collinger K, Moody A, et al.: Non-invasive vascular imaging is associated with cardiovascular risk factors among adolescents with bipolar disorder. Pediatr Cardiol 2015; 36:158–164 [PubMed: 25096903]
28. Levin JB, Krivenko A, Howland M, et al.: Medication adherence in patients with bipolar disorder: A comprehensive review. CNS Drugs 2016; 30:819–835 [PubMed: 27435356]
29. Gitlin MJ,Miklowitz DJ: The difficult lives of individuals with bipolar disorder: A review of functional outcomes and their implications for treatment. J Affect Disord 2017; 209:147–154 [PubMed: 27914248]
30. Kessing LV,Nilsson FM: Increased risk of developing dementia in patients with major affective disorders compared to patients with other medical illnesses. J Affect Disord 2003; 73:261–269 [PubMed: 12547295]
31. Kessing LV, Olsen EW, Mortensen PB, et al.: Dementia in affective disorder: A case-register study. Acta Psychiatr Scand 1999; 100:176–185 [PubMed: 10493083]
32. Kessing LV,Andersen PK: Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and in patients with bipolar disorder? J Neurol Neurosurg Psychiatry 2004; 75:1662–1666 [PubMed: 15548477]
33. Kokmen E, Beard CM, Chandra V, et al.: Clinical risk factors for alzheimer's disease: A populationbased case-control study. Neurology 1991; 41:1393–1397 [PubMed: 1891088]
34. Abcd data exploration and analysis portal,
35. International society for bipolar disoders 2018,

Highlights:

- Research question: what is a practical and efficient approach to pool/integrate clinical research study data focused on aging and bipolar disorder?
- This report describes an initial effort to create an integrated OABD database using the U.S. National Institute of Mental Health Data Archive (NDA), the Aging & Geriatric Experiments in Bipolar Disorder Database (AGE-BD). Goals were to: 1) combine data from 3 U.S. BD studies that included overlapping data elements, 2) investigate research questions related to aims of the original studies, and 3) take an important first step toward combining existing datasets relevant to aging and BD.
- Integrated datasets represent an opportunity to better understand how aging may impact the presentation and evolution of chronic mental health disorders across the life-span.

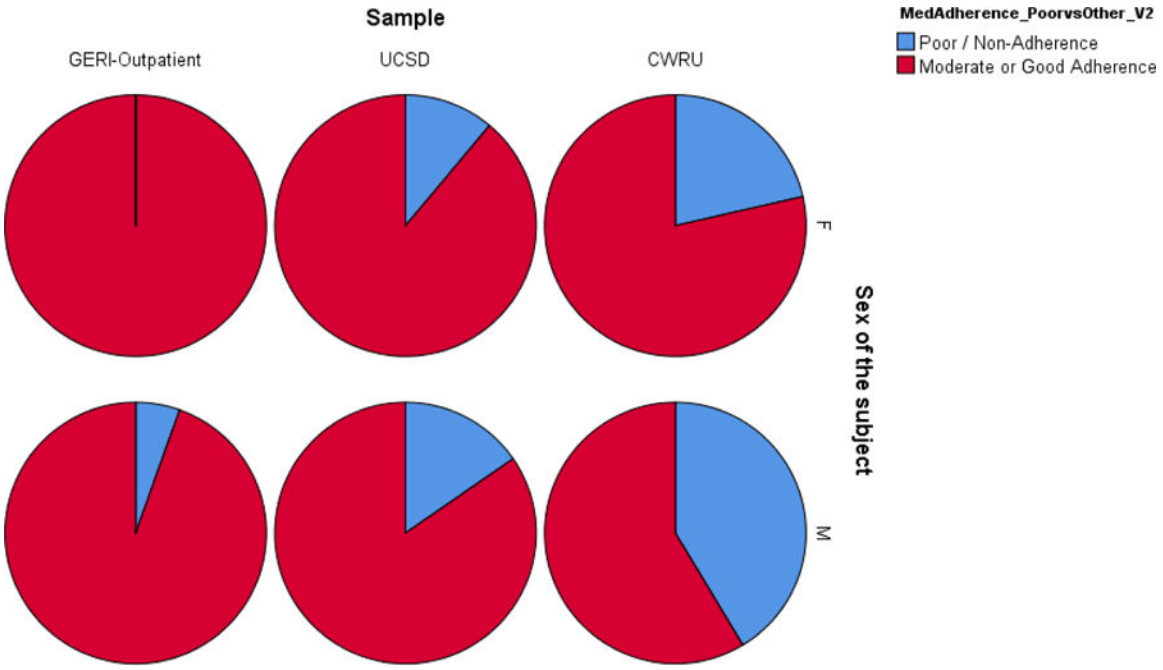

Figure 1.
Proportion of individuals who are poorly adherent with prescribed medication in the AGE-BD sample

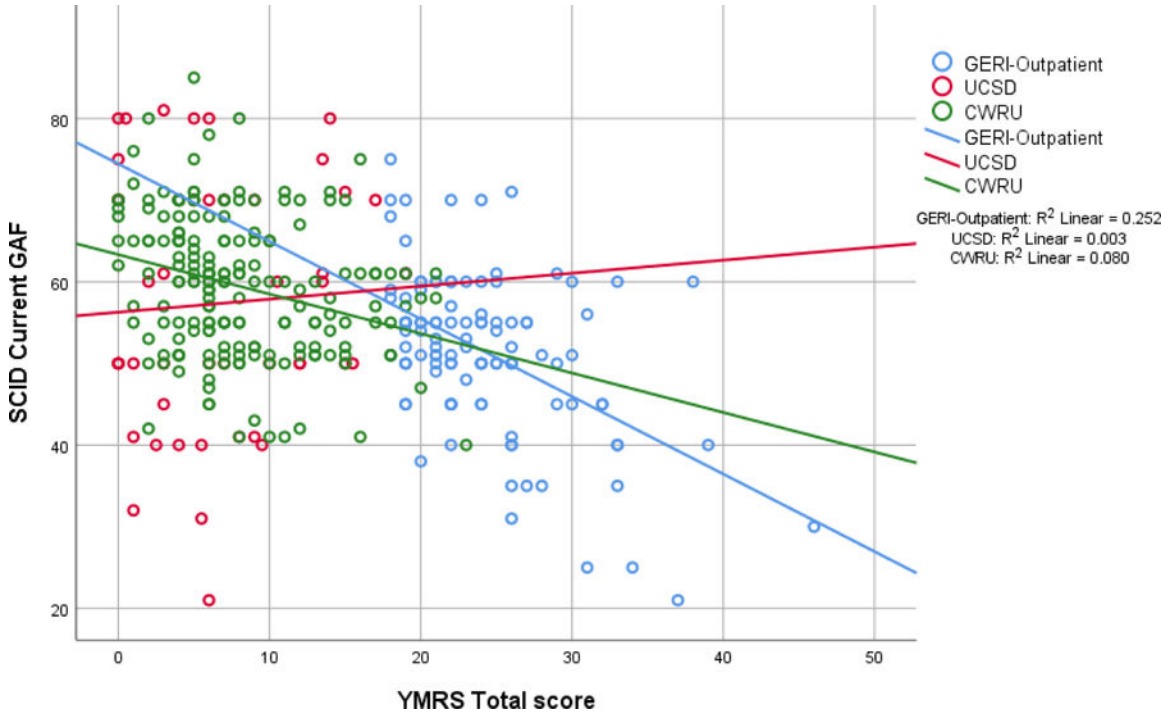

Figure 2a.

Relationship between manic symptoms as measured by the Young Mania Rating Scale (YMRS) and functioning as measured by the Global Assessment of Functioning (GAF) in an integrated dataset of 3 studies of bipolar disorder

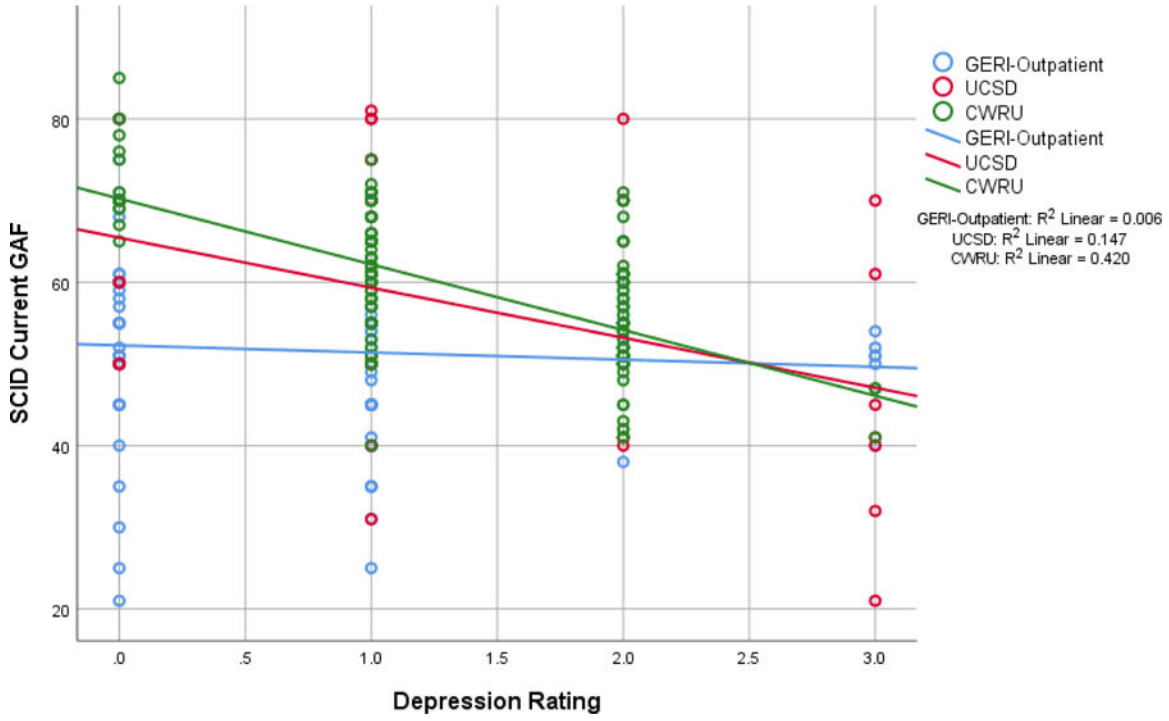

Figure 2b.

Relationship between depressive symptoms as measured by Depression Ratings and functioning as measured by the Global Assessment of Functioning (GAF) in an integrated dataset of 3 studies of bipolar disorder

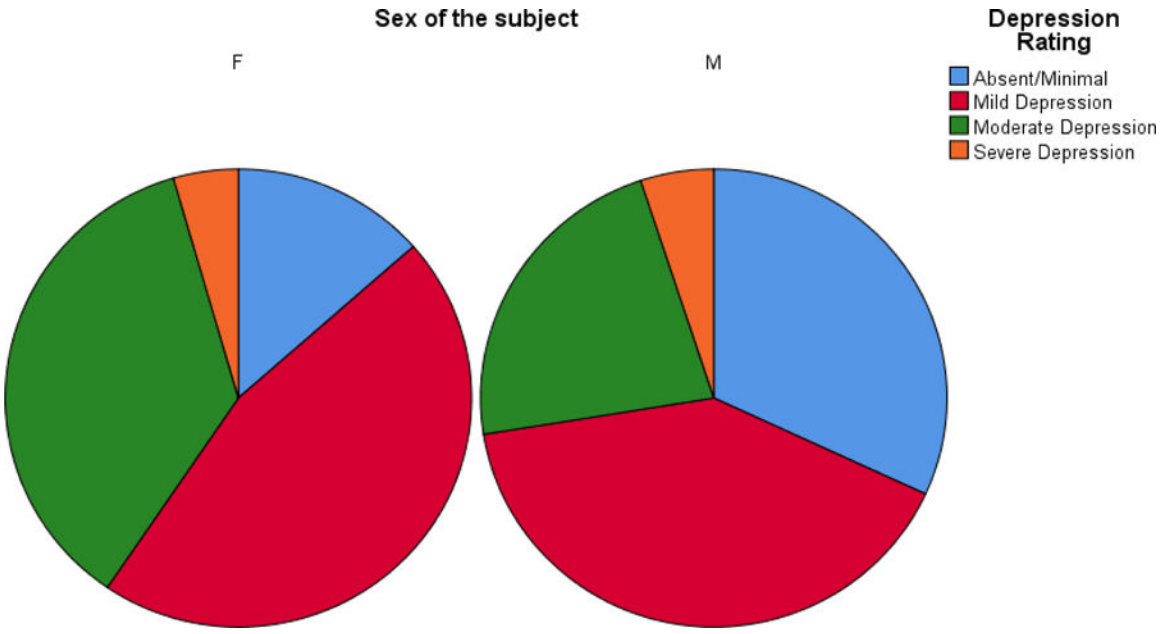

Figure 3.
Depression severity in the AGE-BD sample based on gender

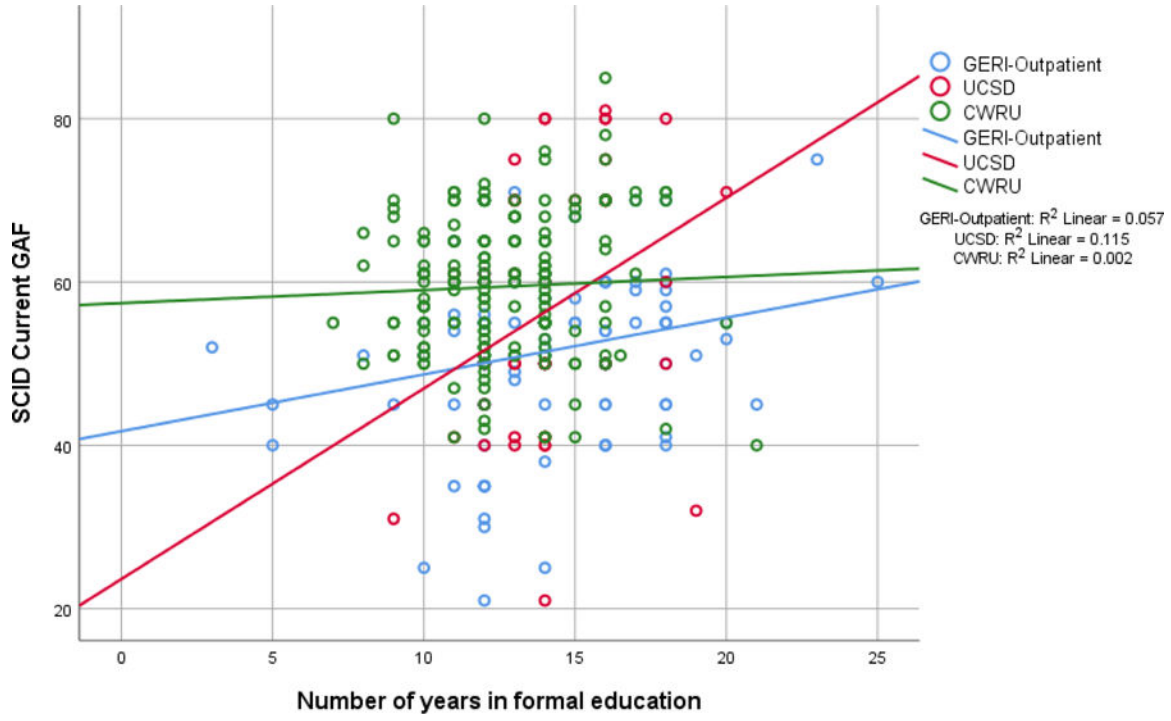

Figure 4.

Relationship between years of education and functioning as measured by the Global Assessment of Functioning (GAF) in an integrated dataset of 3 studies of bipolar disorder

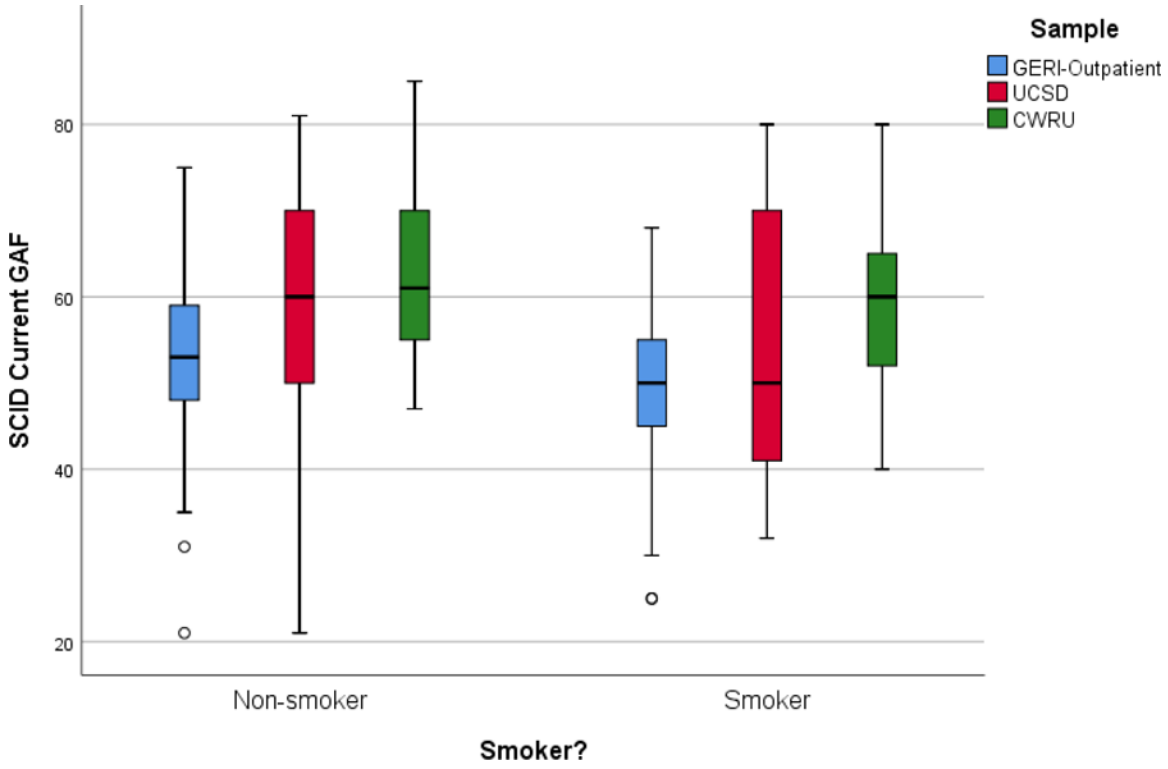

Figure 5.

Relationship between smoking status and functioning as measure by the Global Assessment of Functioning (GAF) in an integrated dataset of 3 studies of bipolar disorder

Table 1:

Comparison of 3 NIMH-funded bipolar disorder clinical study datasets (AGE-BD)

Variables	SD (n=51)		CW (n=184)		GERI-BD Outpatient (n=108)		GERI-BD Inpatient (n=108)		Overall Site Effect		Pairwise differences
	N	Mean (SD) or %	N	Mean (SD) or %	N	Mean (SD) or %	N	Mean (SD) or %	F or χ^2	p	
Age	51	49.8 (7.6)	184	47.7 (10.5)	108	67.3 (6.3)	108	69.0 (6.4)	212.8	<.001	$GERI_i$=$GERI_o$>CW=SD
Gender *Female*	31	61%	126	69%	47	44%	58	54%	18.6	<.001	CW=SD>$GERI_o$; CW>$GERI_i$; SD=$GERI_i$; $GERI_i$=$GERI_o$
Diagnosis *Bipolar I*	47	100%	143	78%	108	100%	108	100%	65.4	<.001	$GERI_i$=$GERI_o$=SD>CW
Race *Caucasian*	36	71%	50	27%	89	82%	99	92%	188.6	<.001	$GERI_i$=$GERI_o$>SD>CW CW>SD=$GERI_o$=$GERI_i$ $GERI_o$=$GERI_i$=CW=SD CW=SD=$GERI_i$=$GERI_o$
African American	10	20%	118	64%	16	15%	8	7%			
Asian	0	0%	0	0%	3	3%	1	1%			
Other	5	10%	16	9%	0	0%	0	0%			
Ethnicity *Hispanic/Latino*	9	18%	6	3%	10	9%	4	4%	16.5	.001	SD>$GERI_i$=CW; SD=$GERI_o$>CW; $GERI_o$=$GERI_i$
Current Smoker	14	27%	106	69%	27	25%	37	34%	62.7	<.001	CW>$GERI_i$=SD=$GERI_o$
Education - Total Years	50	14.3 (2.2)	182	12.7 (2.4)	107	14.2 (3.4)	107	13.2 (3.1)	8.5	<.001	SD=$GERI_o$>CW; $GERI_o$=$GERI_i$; SD=$GERI_i$=CW
Age of Onset	49	17.6 (8.6)	182	24.0 (12.3)	99	29.8 (14.4)	105	34.9 (19.4)	20.8	<.001	$GERI_i$=$GERI_o$>CW>SD
Lifetime Psychiatric Hospitalizations	46	4.2 (8.2)	182	5.2 (7.6)	--	--	--	--	.69	.41	CW=SD
GAF Score	49	57.3 (15.3)	183	59.5 (8.6)	106	51.5 (9.9)	106	36.7 (12.7)	103.6	<.001	SD=CW>$GERI_o$>$GERI_i$
BPRS Score	46	32.7 (7.6)	183	34.6 (7.8)	--	--	---	---	2.1	.15	CW=SD
YMRS Score	48	6.6 (5.3)	182	8.0 (5.0)	108	24.2 (5.2)	108	28.4 (7.6)	389.7	<.001	$GERI_i$>$GERI_o$>CW=SD
Depression Rating	48	1.3 (1.0)	182	1.3 (0.7)	108	0.9 (0.8)	108	0.8 (0.8)	14.5	<.001	SD=CW>$GERI_i$=$GERI_o$
BMI	45	30.9 (6.2)	131	31.7 (8.1)	105	29.5 (6.5)	103	28.4 (4.9)	4.8	.003	CW>$GERI_i$; CW=SD=$GERI_o$; SD=$GERI_o$=$GERI_i$
Medical Condition Categories	43	0.6 (0.9)	184	0.7 (0.8)	96	1.1 (1.1)	95	1.2 (1.1)	11.2	<.001	$GERI_i$=$GERI_o$>CW=SD
Heart Condition	2	4.7%	18	9.8%	34	32%	42	40%	50.3	<.001	$GERI_i$=$GERI_o$>SD=CW
Respiratory Condition	9	20.9%	63	34.2%	34	32%	36	33%	3.2	.37	$GERI_i$=$GERI_o$=SD=CW
Digestive Condition	8	18.6%	26	14.1%	28	26%	28	26%	13.0	.005	$GERI_i$=$GERI_o$>CW; $GERI_i$=$GERI_o$=SD; SD=CW
Renal Condition	2	4.7%	5	2.7%	9	8%	10	9%	7.3	.06	$GERI_i$=$GERI_o$>CW; $GERI_i$=$GERI_o$=SD; SD=CW

Variables	SD (n=51)		CW (n=184)		GERI-BD Outpatient (n=108)		GERI-BD Inpatient (n=108)		Overall Site Effect		Pairwise differences
	N	Mean (SD) or %	N	Mean (SD) or %	N	Mean (SD) or %	N	Mean (SD) or %	F or χ^2	p	
Liver Condition	3	7.0%	7	3.8%	11	10%	10	9%	5.8	.12	$GERI_i$=$GERI_o$>CW; $GERI_i$=$GERI_o$=SD; SD=CW
Total Psychotropic Medications	50	2.7 (1.5)	184	2.3 (1.4)	100	1.0 (1.2)	107	1.7 (1.4)	25.2	<.001	$GERI_i$>$GERI_o$>CW=SD
Total Non- Psychotropic Medications	50	1.6 (2.3)	113	2.3 (1.4)	100	4.6 (3.9)	107	5.8 (3.7)	34.0	<.001	$GERI_i$=$GERI_o$>CW=SD
Total Medications	50	4.3 (2.9)	113	5.0 (2.1)	100	5.7 (4.2)	107	7.5 (4.0)	14.1	<.001	$GERI_i$>$GERI_o$=CW=SD
Medication Adherence ***Week 1***									128.1	<.001	
Poor/Non-Adherence	2	5.6%	85	46.2%	3	2.9%	3	2.9%			CW>SD=$GERI_i$=$GERI_o$
Moderate Adherence	2	5.6%	88	47.8%	2	1.9%	3	2.9%			CW>SD=$GERI_i$=$GERI_o$
Good Adherence	29	82.9%	11	6.0%	99	95%	96	94%			$GERI_i$=$GERI_o$=SD>CW
Week 2									120.0	<.001	
Poor/Non-Adherence	4	11.1%	67	36.4%	4	4%	3	3%			CW>SD=$GERI_i$=$GERI_o$
Moderate Adherence	3	8.3%	66	35.9%	4	4%	7	7%			CW>SD=$GERI_i$=$GERI_o$
Good Adherence	24	66.7%	51	27.7%	83	91%	84	89%			$GERI_i$=$GERI_o$=SD>CW

SD= Sample collected at the University of California San Diego, CW: Sample collected at Case Western Reserve University

GAF= Global Assessment of Functioning, BPRS= Brief Psychiatric Rating Scale 18 item version, YMRS= Young Mania Rating Scale, BMI= Body Mass Index

$GERI_i$= Inpatient sample GERI BD study $GERI_O$ =Outpatient sample GERI BD study

Adherence Week 1: UCSD sample value assessed at week 1, CWRU sample at Screening, GERI BD sample assessed at Day 4

Adherence Week 2: UCSD sample value assessed at week 2, CWRU at baseline, GERI BD sample assessed at Day 14