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Demographic and Clinical Characteristics of Antipsychotic Drug-Treated Older Adults with Bipolar Disorder from the Global Aging & Geriatric Experiments in Bipolar Disorder Database (GAGE–BD)

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ABSTRACT ~ **Objectives:** *Antipsychotic drugs (APS) are widely used to treat patients with bipolar disorder (BD), but there is limited information in older-age bipolar disorder (OABD). This analysis of the Global Aging & Geriatric Experiments in Bipolar Disorder Database (GAGE-BD) investigated characteristics of OABD patients prescribed APS vs. those not prescribed APS.* **Experimental Design:** *The observational analysis used baseline, cross-sectional data from 16 international studies for adults aged ⩾ 50 years with BD comprising 1,007 individuals with mean age 63.2 years (SD = 9.0), 57.4% women, and mean age of onset 31.6 years (SD = 15.0). The dependent variable was current APS treatment status. The independent variables included demographic and clinical variables, and a random effect for study, that were included in generalized mixed models.* **Principal Observations:** *46.6% of individuals (n = 469) were using APS. The multivariate model results suggest that those treated with APS were younger (p = 0.01), less likely to be employed (p < 0.001), had more psychiatric hospitalizations (p = 0.009) and were less likely to be on lithium (p < 0.001). Of individuals on APS, only 6.6% of those (n = 27) were on first-generation antipsychotics (FGAs) and experienced a greater burden of psychiatric hospitalizations (p = 0.012).* **Conclusions:** *APS are widely prescribed in OABD, observed in nearly half of this sample with great variation across sites. Individuals with OABD on APS have more severe illness, more frequent hospitalizations and are more often unemployed vs. those not on APS. Future studies need to examine longitudinal outcomes in OABD prescribed APS to characterize underlying causal relationships.* Psychopharmacology Bulletin. *2022;52(2):8–33.*

Introduction

Individuals with older-age bipolar disorder (OABD) are increasing with the growing proportion of elderly individuals world-wide.[1,2] Mood stabilizers and/or antipsychotic drugs (APS) are commonly used to treat individuals with bipolar disorder (BD) in both the general adult population and in OABD.[3–5] While mood stabilizers, especially lithium and divalproex, have been studied in OABD,[2,6,7] information on APS is limited. Evidence on APS use in OABD is derived from modestly-sized secondary analyses in mixed-age adult bipolar patients, open-label trials, and case series.[8–10]

The Global Aging & Geriatric Experiments in Bipolar Disorder Database (GAGE-BD) is a pooled and integrated OABD-focused database that provides a unique opportunity to study APS use and its associated factors in OABD.[11] Within the GAGE-BD data set, we describe demographic and clinical characteristics of OABD patients actively treated with APS versus not treated with APS. We examined APS status in relation to age, gender, age of onset, number of recent hospitalizations, number of somatic or psychiatric comorbidities, rapid cycling, substance abuse, and cognitive performance. In the APS group, we also examined use of first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs). We hypothesized that individuals with OABD on APS would have more severe BD and more somatic burden.

Materials and Methods

Overview

The GAGE-BD sample consists of pooled data from multiple archival studies. The methods of GAGE-BD have been previously described.[11] The aggregate sample for this analysis, as of March 2020, used baseline, cross-sectional data from 16 international studies reporting data on adults ages 50 years and older with BD (n = 1,007). Studies that contributed data are listed in Supplemental Tables 1 and 2. Approval to contribute data was obtained by local site institutional review boards or ethics committees at originating sites as appropriate.

Dependent Variable

APS exposure was defined as being on current oral APS treatment (vs. no oral APS treatment). Individuals were then classified as being on an FGA if they were on either FGA monotherapy or if they were on poly-drug APS regimens that included an FGA.

Independent Variables

We examined demographic (age, gender, education level, employment status) and clinical associated variables of current oral APS use versus non-use. Clinical characteristics included: age of BD onset in years; Type I vs. II BD; number of past psychiatric hospitalizations; rapid cycling; manic symptom severity; depressive symptom severity; functional status; somatic comorbidity; body mass index (BMI); cognitive performance; current lithium use. Within the APS group, we also examined the above associated variables for the type of APS (FGA vs. SGA) and current chlorpromazine (CPZ) equivalence daily dosage.

Measures

Diagnostic and clinical course information was gathered in a variety of ways across studies, including structured clinical interviews, chart review, and self-report.

Manic symptom severity was measured using the Young Mania Rating Scale (YMRS) total score.[12] Functional status was assessed using the Global Assessment of Functioning (GAF).[13] Depressive symptom severity was grouped into 3 ordinal severity categories derived by converting total scores from either the Hamilton Depression Rating Scale (HAM-D),[14] the Montgomery-Asberg Depression Rating Scale

(MADRS),[15] or the Center for Epidemiologic Studies Depression Scale (CES-D).[16] Categories were calculated based on clinical cutoffs as follows: no depression (HAM-D: 0–7, MADRS: 0–6, CES-D: 0–15); mild-moderate depression (HAM-D: 8–23, MADRS: 7–34, CES-D: 16–27); and severe depression (HAM-D $\geqslant$ 24, MADRS $\geqslant$ 35, CES-D $\geqslant$ 16).

Somatic comorbidity was assessed in individual studies using a variety of methods, including standardized measures such as the Cumulative Illness Rating Scale (CIRS)[17] and the Charlson Comorbidity Index[18] or clinical determination of selected comorbidity categories based on self-report, charts, or examination. Somatic comorbidity was harmonized into 8 binary variables (present/not present)[19] within the following domains: cardiovascular, respiratory, gastrointestinal, liver, renal, genitourinary, musculoskeletal, and endocrine. Summing across these 8 categories was used to construct a total somatic comorbidity burden variable.

CPZ dosage equivalents for oral APS were calculated using recommendations of the College of Psychiatric and Neurologic Pharmacists (CPNP).[20] Cognitive performance was measured using the Mini-Mental State Examination.[21]

Data Analysis

The predictor variables for APS exposure and for FGA vs. SGA were examined using generalized mixed-effect regression models with a random effect for study cohort to account for meta-data differences between studies. Initial models with only site study cohort as a random effect were used to calculate odds ratios for each predictor; for significant predictors, full models were also tested that included the following covariates: age (added to models that did not already have age), gender, age of onset, BD I vs. BD II (added to models that did not already have BD I vs. BD II), manic symptom severity and depressive symptom severity to control for severity and type of mood symptoms. All continuous outcome variables were examined for normality of distribution; no transformations were required. All analyses were carried out in IBM SPSS version 28. For all analyses, a two-sided alpha of 0.05 was considered statistically significant.

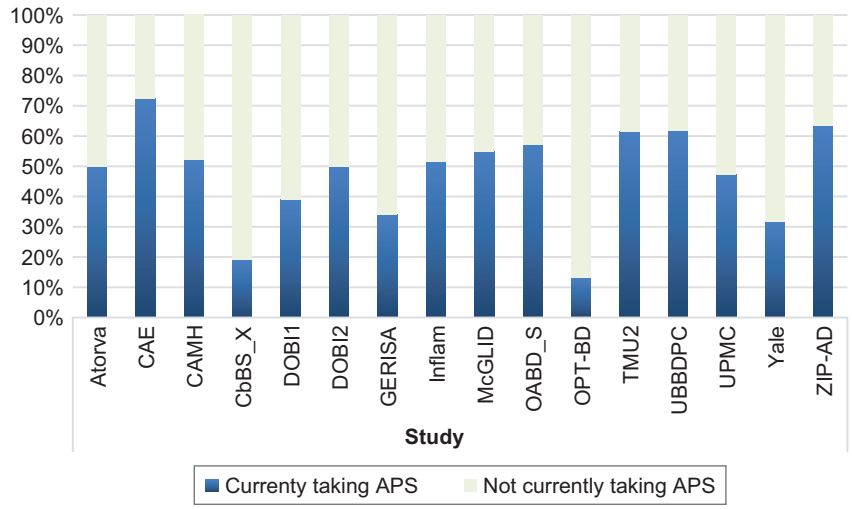
Results

Overall Sample

Figure 1 shows the proportions of APS and no APS subgroups from each site study cohort. APS use varies from site to site with lowest (13%) in the OPT to highest (72%) in the CAE.

FIGURE 1

Proportion of OABD on APS by Study



The entire sample comprised 1,007 individuals, mean age 63.2 years (SD = 9.0), including 578 females (57.4%),776 (74.4%) with type I BD, and age of onset mean 31.6 years (SD = 15.0). As noted in Table 1, there were 469 (46.6%) individuals in the APS group. In analyses controlling only for a random effect of site study cohort, individuals on APS were younger (Odds Ratio [95% Confidence Interval] = 0.97 [0.95–0.99]), less likely to be employed (0.40 [0.26–0.62]), less likely to be BD II (0.61 [0.44–0.85]), had more past psychiatric hospitalizations (1.07 [1.02–1.12]), were less likely to have musculoskeletal comorbidities (0.65 [0.46–0.91]) and less likely to also be prescribed lithium (0.58 [0.43–0.77]). Other demographic and clinical variables did not significantly predict APS vs. non-APS group membership.

In models that included a random effect of site study cohort and fixed-effects covariates (age, gender, BD type I vs. BD type II, age of onset, manic and depressive symptom severity), variables that remained as significant predictors of APS vs. non-APS group membership were age (0.96 [0.94–0.99]), employment status (0.35 [0.22–0.55]), previous hospitalizations (1.07 [1.02–1.13), and lithium use (0.50 [0.34–0.74]). Musculoskeletal comorbidities (0.86 [0.55–1.30]) and BD I vs. BD II (0.95 [0.60–1.50]) were no longer significant predictors in the context of the multivariate model.

Sub-Group on APS

Table 2 shows demographic and clinical characteristics of individuals prescribed FGA monotherapy or poly-drug APS regimens that

TABLE 1

Characteristics of OABD Prescribed vs. Not Prescribed Antipsychotic Medications (APS), Odds Ratio and Significance of Predictors

VARIABLE	ENTIRE SAMPLE N = 1,007	APS N = 469	NOT ON APS N = 538	ODDS RATIO FOR APS VS. NOT ON APS (95% CONFIDENCE INTERVAL)	PREDICTOR T-VALUE, P-VALUE FROM GENERALIZED LINEAR MIXED MODEL WITH RANDOM EFFECT OF STUDY
Demographic variables					
Age (mean/SD)	63.16 (9.0)	61.38 (8.4)	64.71 (9.2)	.97 (.95–.99)	**t = −3.31, p < .001***
Gender (N/%Men)	429 (42.6)	199 (42.4)	230 (42.8)	.97 (.74–1.26)	t = −0.25, p = .80
Education in years (mean/SD)	12.81 (3.8)	12.77 (3.6)	12.85 (4.0)	.99 (.95–1.03)	t = −0.44, p = .66
Employed (N/%)	146 (24.6)	47 (15.8)	99 (33.3)	.40 (.26–.62)	**t = −4.21, p < .001***
Clinical variables					
BD Type (N/% BD II)	235 (25.6)	91 (21.9)	144 (28.7)	.61 (.44–.85)	**t = −2.97, p < .01**
Age of onset (mean/SD)	31.55 (15.0)	30.41 (14.2)	32.56 (15.7)	1.0 (.98–1.01)	t = −0.97, p = .33
Past psychiatric hospitalizations (mean/SD)	3.36 (5.1)	4.12 (6.1)	2.66 (3.7)	1.07 (1.02–1.12)	**t = 2.99, p < .01***
Somatic Comorbidity (N/%)					
– Cardiovascular	422 (45.2)	183 (42.7)	239 (47.3)	.82 (.61–1.11)	t = −1.28, p = .20
– Respiratory	289 (34.5)	131 (34.5)	158 (34.6)	.88 (.61–1.26)	t = −0.71, p = .48
– Gastrointestinal	180 (25.0)	87 (24.4)	93 (25.7)	1.03 (.71–1.51)	t = 0.17, p = .86
– Hepatic/Pancreatic	54 (7.6)	30 (8.5)	24 (6.8)	1.45 (.81–2.59)	t = 1.24, p = .22
– Renal	45 (7.2)	22 (6.9)	23 (7.5)	.95 (.50–1.78)	t = −0.17, p = .87
– Genito-urinary	107 (20.1)	43 (17.0)	64 (22.9)	.73 (.45–1.20)	t = −1.24, p = .22
– Musculoskeletal	305 (40.2)	136 (35.7)	169 (44.7)	.65 (.46–.91)	**t = −2.50, p = .01**
– Endocrine	332 (35.5)	147 (37.0)	185 (36.7)	.92 (.68–1.24)	t = −0.57, p = .57
– Total number of comorbidities	1.85 (1.7)	1.8 (1.7)	1.89 (1.8)	.92 (.82–1.02)	t = −1.60, p = .11

Continued

TABLE 1 (*Continued*)

CHARACTERISTICS OF OABD PRESCRIBED VS. NOT PRESCRIBED ANTIPSYCHOTIC MEDICATIONS (APS), ODDS RATIO AND SIGNIFICANCE OF PREDICTORS

VARIABLE	ENTIRE SAMPLE N = 1,007	APS N = 469	NOT ON APS N = 538	ODDS RATIO FOR APS VS. NOT ON APS (95% CONFIDENCE INTERVAL)	PREDICTOR T-VALUE, P-VALUE FROM GENERALIZED LINEAR MIXED MODEL WITH RANDOM EFFECT OF STUDY
Rapid cycling (N/%)	67 (14.7)	40 (20.2)	27 (10.4)	1.66 (.89–3.10)	t = 1.61, p = .11
MMSE (mean/SD)	27.57 (2.9)	27.37 (2.9)	27.69 (2.8)	1.01 (.93–1.09)	t = 0.21, p = .83
BMI (mean/SD)	29.38 (7.1)	29.19 (7.0)	29.54 (7.2)	.99 (.97–1.02)	t = −0.62, p = .54
Depressive symptom severity (N/%)					
– No depression	496 (60.4)	213 (56.8)	283 (63.5)	–	–
– Mild to moderate	294 (35.8)	148 (39.5)	146 (32.7)	1.25 (.87–1.8)	t = 1.22, p = .22
– Severe	31 (3.8)	14 (3.7)	17 (3.8)	1.13 (.52–2.48)	t = 0.30, p = .76
YMRS (mean/SD)	3.76 (5.3)	3.64 (4.6)	3.86 (5.9)	.98 (.95–1.01)	t = −1.27, p = .20
GAF (mean/SD)	61.99 (12.7)	61.74 (12.1)	62.23 (13.2)	.99 (.96–1.01)	t = −0 .96, p = .34
Concomitant lithium (N/%)	413 (41.6)	161 (34.8)	252 (47.6)	.58 (.43–.77)	**t = −3.68, p < .001***

*Also significant after controlling for fixed effects covariates (age, gender, age of onset, BD I vs. BD II, YMRS and depression severity).
MMSE, Mini-mental State Examination (total); BMI, Body mass index; YMRS, Young Mania Rating Scale Score (total); GAF, Global Assessment of Functioning.

TABLE 2

Characteristics of OABD Prescribed Any First Generation (FGA) or Only a Second Generation (SGA) APS, Odds Ratio and Significance Of Predictors

GROUPS	SGA N = 385	FGA[a] N = 27	ODDS RATIO FOR ANY SGA ONLY VS. ANY FGA (95% CONFIDENCE INTERVAL)	PREDICTOR T-VALUE, P-VALUE FROM GENERALIZED LINEAR MIXED MODEL WITH RANDOM EFFECT OF STUDY
Specific drug types N/%[b]	Quetiapine 180 (44.1) Olanzapine 89 (21.8) Aripiprazole 55 (13.5) Risperidone 48 (11.8) Ziprasidone 12 (2.9) Asenapine 7 (1.7) Clozapine 7 (1.7) Lurasidone 5 (1.2) Paliperidone 4 (1.0) Clotiapine 1 (0.2)	Haloperidol 16 (59.2) Perphenazine 4 (14.8) Bromperidol 1 (3.7) Flupentixol 1 (3.7) Loxapine 1 (3.7) Penfluridol 1 (3.7) Trifluoperazine 1 (3.7) Zuclopenthixol 1 (3.7) Chlorpromazine 1 (3.7)	–	–
CPZ equivalents (combined for each FGA and/or SGA class; mean/SD)	203.57 (193.3)	362 (380.1)	0.998 (.996–1.00)	**t = –2.18, p = .03**
Age (mean/SD)	61.25 (8.4)	61.77 (10.2)	1.02 (.96–1.08)	t = 0.53, p = .60
Gender (N, % Male)	168 (43.9)	13 (48.1)	1.32 (.59–2.97)	t = 0.68, p = .50
Education (mean/SD)	12.83 (3.5)	12.71 (3.3)	1.00 (.88–1.14)	t = 0.04, p = .97
Employed (N, %)	46 (16.4)	1 (10)	1.26 (.26–6.04)	t = 0.29, p = .77
BD Type (N/% BD II)	84 (24.5)	0 (0.0)	--	--
Age of onset (mean/SD)	30.25 (14.3)	27.48 (8.8)	1.02 (.99–1.06)	t = 1.18, p = .24
Past psychiatric hospitalizations (mean/SD)	3.73 (5.6)	11.27 (10.5)	.91 (.86–.97)	**t = –3.13, p < .01***
Somatic Comorbidity: (N,%)				
– Cardiovascular	131 (36.9)	5 (27.8)	1.65 (.55–4.95)	t = 0.89, p = .37
– Respiratory	90 (28.8)	5 (27.8)	1.23 (.38–4.01)	t = 0.34, p = .74

Continued

TABLE 2 (*Continued*)

CHARACTERISTICS OF OABD PRESCRIBED ANY FIRST GENERATION (FGA) OR ONLY A SECOND GENERATION (SGA) APS, ODDS RATIO AND SIGNIFICANCE OF PREDICTORS

GROUPS	SGA N = 385	FGA[a] N = 27	ODDS RATIO FOR ANY SGA ONLY VS. ANY FGA (95% CONFIDENCE INTERVAL)	PREDICTOR T-VALUE, P-VALUE FROM GENERALIZED LINEAR MIXED MODEL WITH RANDOM EFFECT OF STUDY
– Gastrointestinal	58 (19.7)	3 (21.4)	.94 (.28–3.11)	t = –0.10, p = .92
– Hepatic/Pancreatic	14 (4.8)	4 (30.8)	.17 (.05-.61)	**t = –2.76, p < .01**
– Renal	16 (6.2)	0 (0.0)	1.98 (.10–39.66)	t = 0.45, p = .65
– Genito-urinary	23 (11.9)	1 (10.0)	1.12 (.17–7.37)	t = 0.12, p = .91
– Musculoskeletal	100 (32.1)	5 (35.7)	.91 (.33–2.50)	t = – 0.18, p = .85
– Endocrine	105 (29.3)	2 (11.1)	1.78 (.60–5.31)	t = 1.04, p = .30
– Total # medical comorbidities	1.5 (1.4)	1.39 (1.5)	1.11 (.76–1.63)	t = 0.56, p = .58
Rapid cycling (N/%)	35 (19.1)	4 (23.5)	.64 (.18–2.28)	t = –0.69, p = .49
MMSE (mean/SD)	27.47 (2.8)	28.2 (2.2)	.88 (.67–1.16)	t = –0.90, p = .37
BMI (mean/SD)	28.92 (7.2)	27.27 (5.7)	1.03 (.94–1.12)	t = 0.65, p = .52
Depressive severity (N, %)				
– No depression	164 (53.4)	9 (50.0)	–	–
– Mild to moderate	132 (42.9)	7 (38.9)	.86 (.29–2.58)	t = –0.27, p = .79
– Severe	12 (3.9)	2 (11.1)	.31 (.05–1.72)	t = –1.35, p = .18
YMRS (mean/SD)	3.76 (4.7)	3.09 (4.4)	1.01 (.91–1.13)	t = 0.22, p = .83
GAF (mean/SD)	61.40 (12.3)	63.67 (10.0)	1.00 (.95–1.05)	t = –0.02, p = .98
Concomitant lithium (N/%)	134 (35.3)	14 (51.8)	.51 (.22–1.17)	t = –1.59, p = .11

[a]Includes individuals on FGA monotherapy as well as those who had an FGA included in a polydrug APS regimen; SGA drugs included in FGA + SGA group: Aripiprazole, Quetiapine, Risperidone, Clozapine, Olanzapine.
[b]Total > 100% if individuals were on multiple APS.
*Also significant after controlling for fixed effects covariates.
MMSE, Mini-mental State Examination (total); BMI, Body mass index; YMRS, Young Mania Rating Scale Score (total); GAF, Global Assessment of Functioning.

included an FGA. Information on type of antipsychotic (SGA or FGA) was available for N = 412. Of those, just 27 (6.6%) used FGAs. The most prescribed FGAs were haloperidol (59.2% of total FGA prescriptions) and perphenazine (14.8%). The most prescribed SGAs were quetiapine (44.1% of SGAs), olanzapine (21.8%) and aripiprazole (13.5%).

Mean dose of CPZ equivalents was higher in the FGA group than in the SGA group (0.998 [0.996–1.00]). Compared with those on FGA, those on SGAs had fewer past hospitalizations (0.91 [0.86–0.97]) and less hepatic/pancreatic comorbidity (0.17 [0.05–0.61]). However, after covariates were included in the models, CPZ equivalents (1.001 [0.996–1.006]) and hepatic/pancreatic comorbidities (0.37 [0.07–1.9]) were no longer significantly associated with use of FGA vs. SGA prescription; the only significant association was a greater number of past psychiatric hospitalizations among those prescribed FGAs (0.93 [0.88–0.98]).

Discussion

In our analysis of 16 pooled international research studies examining APS use in OABD, about half of the pooled OABD sample (46.6%) were on APS. Most APS prescriptions were for SGAs (more than 93%) with lithium prescribed less in OABD subjects who were on APS. Our hypotheses that individuals on APS would have more severe BD and more somatic burden were only partially confirmed. Most demographic and clinical variables were the same among OABD prescribed vs. not prescribed APS and there were no differences in somatic burden between the APS and no APS groups. However, after controlling for site study cohort and covariates, notable differences between the two groups were that those on APS were younger, less likely to be employed, less on lithium and had more psychiatric hospitalizations. Additionally, those on FGA had more psychiatric hospitalizations vs. those on SGA.

There are several clinical implications of our findings. First, findings suggest that OABD who are prescribed APS may have more severe illness given their more frequent hospitalizations and lower likelihood of being employed, assuming that employment is a proxy for longer-term functional level. Those on FGAs were particularly likely to have more previous hospitalizations. Treatment guidelines for management of individuals with BD in settings where they are more likely to present with mania, agitation or more severe symptoms suggest that combination treatments that include an APS may be effective more quickly than standard non-APS mood stabilizers.[5,22]

We also found that lithium is prescribed less in OABD subjects who are on APS. It is possible that clinicians do not prescribe lithium in patients who may not be able to manage the procedures required for

appropriate lithium monitoring (e.g. illness severity or other characteristics may make it difficult to get regular bloodwork) and instead the clinicians may choose an antipsychotic over lithium given the relatively broader short-term toxicity profile. It is also possible that APS could have been started while individuals were being treated in inpatient settings or in the acute phase and perhaps APS was continued as part of maintenance care. It is less clear how long individuals with BD, especially if they are older and more prone to medication side effects generally, should be continued on APS and/or whether their dosage should be modified over time. In the latest Canadian Network for Mood and Anxiety (CANMAT) treatment guideline, olanzapine is removed as a first-line agent for maintenance treatment of BD as the result of the concern on safety issues.[23] A recent 6-year retrospective cohort study from 6 U.S. states analyzed the impact of APS dose reduction in patients with BD and major depressive disorder and evaluated survival analyses with matched controls receiving a stable dosage.[24] Results showed that patients who had APS reductions showed small but statistically significant increases in all-cause and mental health-related hospitalizations. There is clearly a need for additional long-term studies regarding the necessity and safety of maintenance APS in OABD.[25]

Our findings also demonstrate that OABD prescribed APS are younger than those not prescribed APS. This could reflect the possibility that clinicians may hesitate to prescribe APS to older patients. Given the U.S. Food and Drug Administration (FDA) warnings regarding increased risk of mortality associated with the use of both FGA and SGAs for management of dementia-related neuropsychiatric behaviors,[26,27] there is logical concern related to mortality risk of APS in other later-life psychiatric conditions. A study by Bhalerao and colleagues used national VA data to examine the risks of mortality with commonly used individual SGAs, with a focus on OABD starting a new SGA prescription.[28] Findings suggested some differential risks across APS compounds, with risperidone having the highest risk among the individual SGAs and quetiapine having the lowest risk. An important caveat is that the authors suggest that findings could have been biased by "sicker" individuals being prescribed risperidone vs. other drugs. While quetiapine was the most prescribed SGA within the global OABD sample reported here, it is not entirely clear what is driving clinician prescribing behavior in OABD. Similarly, prescribing clinicians might be reluctant to prescribe lithium with APS due to concerns about cumulative side effects and tolerability,[29] even when patient's attitudes towards lithium are favourable.[30,31]

An additional important element of the findings is the number of notable variables that were not different between OABD prescribed

vs. not prescribed APS. For example, we did not find differences in body mass index (BMI) or somatic comorbidity once covariates were included in analytic models, results that seemed a bit surprising given the weight gain and metabolic or other effects common to APS. Perhaps older people on APS have stabilization of weight or other medication-related side effects over time.[32] Alternatively, it is possible that individuals who have more severe weight increases or metabolic abnormalities on APS do not stay on these medications long-term and the APS sub-group might represent a sample of who have had minimal drug-related adverse effects (a healthy survivor bias in our sample). Similarly, the lack of difference between the APS vs. no APS group on current functional status as measured by GAF could suggest that our APS sub-group had a good response to APS and were thus maintained on this treatment because the benefit outweighed the burden or side effects associated with treatment.

While this analysis is important because of the relatively large sample size and international representation, it also has limitations that restrict generalizability. Perhaps most critical is that cross-sectional analysis cannot infer causality (Vieta & Angst, 2021).[33] For example, clinicians may bias prescribing based on tolerability concerns, therefore avoiding initiation of APS for certain patients. Additionally, it is not clear whether the finding of similar medical comorbidity between APS and non-APS groups indicated that APS have limited impact on somatic burden in OABD vs. the possibility that individuals who had more severe early side effects from APS did not continue APS. While the GAGE-BD project has several clinically important variables such as manic and depressive symptom severity, the currently available data do not include other important information such as overall illness severity, psychotic symptoms, relapse episodes, or previous cumulative APS exposure. While past psychiatric hospitalizations are a rough proxy for longer-term illness severity, there are factors beyond symptoms and relapse that may drive the decision to hospitalize a person with BD. Finally, research samples may not represent the broader population of OABD.

A future analysis of a larger GAGE-BD database may go beyond the current dataset enabling examination of the association between APS use and OABD recovery outcomes such as relapse and functional status as well as safety. These types of analyses require longitudinal data. The GAGE-BD project team is in the process of importing, cleaning, and harmonizing repeated measures within our broader sample that ideally will help answer some of the questions identified in the findings presented here.

Conclusions

APS are commonly prescribed among OABD (about half of the pooled sample) with significant variation across study sites. APS may be used for individuals with more severe BD though causal effect needs to be clarified in longitudinal studies. Findings from this large global sample can inform longitudinal outcomes analyses to identify causal effects vs. prescriber/patient preference vs. selective cohort effects in relation to the use of APS in OABD. ✤

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Supplemental Material

SUPPLEMENTAL TABLE 1

Metadata from GAGE-BD Participating Studies

FULL NAME OF STUDY	NICKNAME	SITE	TOTAL N	STUDY DESIGN	STUDY DRUG, IF ANY
Atorvastatin for the Treatment of Lithium-Induced Nephrogenic Diabetes Insipidus: A Randomized Controlled Trial	Atorvastatin	Lady Davis Institute	13	RCT	Atorvastatin
Treatment Adherence Enhancement in Bipolar Disorder	CAE	Case Western Reserve University (multi-site study)	184	RCT	None
Cognition in Bipolar Disorder XR	CiBS-XR	GGZ inGeest	197	Observational	None
Cognition in Euthymic Older Adults with Bipolar Disorder	CAMH	Center for Addiction & Mental Health	48	Observational	None
Dutch Older Bipolar cohort, wave 2012	DOBi1	GGZ inGeest	101	Observational	None
Dutch Older Bipolar cohort, wave 2017–18	DOBi2	GGZ inGeest	69	Observational	None
Open-label, prospective trial of lamotrigine for Symptoms of Geriatric bipolar Depression	GERI-SAD	Case Western Reserve University	53	Prospective uncontrolled intervention	Lamotrigine
Dynamic Inflammatory and Mood Predictors of Cognitive Aging in Bipolar Disorder	Inflamm-aging	University of California San Diego	168	Observational	None
The McGill Geriatric Lithium-Induced Diabetes Insipidus Clinical Study	McGLIDICS	McGill University	100	Observational	None

Cognitive Impairment and dementia in late life bipolar disorder	OABD	University of Sao Paulo	144	Observational	None
Asenapine in the Treatment of Older Adults With Bipolar Disorder	OPT-BD	Case Western Reserve University	15	Prospective uncontrolled intervention	Asenapine
Taipei Medical University	TMU 2	Taipei Medical University	43	Observational	None
University of Barcelona Bipolar Disorder Program Cohort	UBBDPC	University of Barcelona	136	Observational	None
The Effect of Bipolar Disorder and its Comorbidities on Cognition in Older Adults	UPMC	University of Pittsburgh Medical Center	149	Observational	None
Mood Disorders Research Program Database	Yale	Yale School of Medicine	88	Observational	None
Ziprasidone switching in response to adherence in psychotropic-related weight gain concerns among patients with bipolar disorder	ZIP-AD	Case Western Reserve University	30	Prospective uncontrolled intervention	Ziprasidone

RCT = Randomized controlled trial.

SUPPLEMENTAL TABLE 2

Individual Study Inclusion and Exclusion Criteria

STUDY NICKNAME	INCLUSION CRITERIA	EXCLUSION CRITERIA
Atorvastatin	1. Individuals of 18 years of age or older (including patients 18–64 and 65+, with no maximum age limit) 2. Individuals with bipolar disorder in any phase of illness: euthymic, depressed, or hypomanic. Patients were recruited from the outpatient bipolar and geriatric psychiatry clinics 3. Able and willing to give informed consent 4. Chronic and current lithium users (at least 2 months of Lithium use) 5. Stable dose of lithium for the past 2 months.—Patients taking any lithium level will be included 6. In the original study, patients with any psychiatric diagnosis were included, and had either bipolar disorder (n = 54) or unipolar depression (n = 6). Only patients with bipolar disorder who re-consented to data sharing with GAGE-BD were included in the current GAGE-BD analysis. 7. Patients were included in the atorvastatin trial if they had partial or complete nephrogenic diabetes insipidus (NDI)—defined as a 10-hour water restriction urine osmolality (UOsm) ⩽ 300mOsm/Kg	1. Patients with statin use within 6 weeks prior to the study 2. Patients with a past history of severe adverse reaction to statins 3. Patients with a baseline Low Density Lipoprotein (LDL) level < 1.5 4. Relative contraindications to statin use 42: pregnancy or lactation, concurrent use of fibrates, heavy ethanol consumption (> 50 units/week) 5. Incapacity to consent 6. Deemed by the treating physician to have a severe cognitive or behavioural disturbance such as acute delirium or moderate-severe DSM5 Neurocognitive Disorder (dementia), preventing their ability to complete safely the study questionnaire and/or to provide blood and urine test.
CAE	1. Subjects must have type I or type II Bipolar Disorder (BD) as confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)	1. Unable or unwilling to participate in psychiatric interviews. This will include individuals, who may be too psychotic to participate in interviews/rating scales

(Continued)

SUPPLEMENTAL TABLE 2 (*Continued*)

Individual Study Inclusion and Exclusion Criteria

STUDY NICKNAME	INCLUSION CRITERIA	EXCLUSION CRITERIA
	2. Have had BD for at least two years duration 3. Have received treatment with at least one evidence-based medication to stabilize mood for at least six months (lithium, anticonvulsant, or antipsychotic mood stabilizer) 4. Either 20% or more non-adherent with current BD medication treatment (i.e. lithium, anticonvulsant, or antipsychotic mood stabilizer) 5. Be able to participate in psychiatric interviews	2. Unable or unwilling to give written, informed consent to study participation 3. Children under the age of 18 4. Individuals at high risk for suicide who cannot be safely managed in their current treatment setting
CiBS-XR	1. 60+ years old 2. Diagnosis of bipolar I or bipolar II 3. Outpatients 4. Euthymic for at least 3 weeks as assessed by patient's psychiatrist 5. No history of ECT Control group: 1. 60+ years old 2. No current or lifetime psychiatric illness or addict	1. Not euthymic as assessed by YMRS, CESD 2. History of ECT 3. Alcohol dependency or substance abuse 4. Dementia Controls: 1. History of psychiatric illness or addiction 2. Recent memory complaint
CAMH	1. Age 50 years and above 2. Meets DSM-IV TR criteria for a current diagnosis of Bipolar I or II Disorder 3. Willingness and ability to speak English 4. Willingness to provide informed consent 5. Corrected visual ability that enables reading of newspaper headlines and hearing capacity that is adequate to respond to a raised conversational voice.	1. Does not meet criteria for any type of dementia or other neurological disorder affecting the central nervous system (for example, multiple sclerosis, history of traumatic brain injury, cerebrovascular disease) 2. No history of schizophrenia, schizoaffective or other psychotic disorders 3. No alcohol or other drug abuse/ dependence within 6 months of testing 4. No Electroconvulsive Therapy (ECT) within 6 months of testing.

(Continued)

SUPPLEMENTAL TABLE 2 (*Continued*)

Individual Study Inclusion and Exclusion Criteria

STUDY NICKNAME	INCLUSION CRITERIA	EXCLUSION CRITERIA
	6. At time of assessment they should be clinically euthymic for four weeks preceding study entry, with both HRSD-17 and YMRS scores of 10 or less at time of assessment (The criteria are selected to capture bipolar disorder across the older adults. We are interested in bipolar I and II disorder to capture bipolar illness that would generalize to "real-world," clinical practice. Although there are no set criteria for designating "acceptable" euthymia by HRSD-17 and YMRS, there is growing consensus among geriatric psychiatrists that scores 10 or less on these instruments are indicated to minimize acute impact of mood symptoms when performing NP testing).	
DOBi1	1. Age ⩾ 60 years 2. Diagnostic procedure (MINI) indicates BPI, BPII, or BP NOS 3. Willing to give consent (some consented to chart review plus structured interview, others consented to chart review only)	1. Dementia 2. Intellectual disability (IQ < 70) 3. Language barrier 4. Poor cognitive functioning (measured by Mini Mental State Examination; MMSE < 18 5. Insufficiently stable psychiatric condition
DOBi2	1. Age ⩾ 50 years 2. Diagnostic procedure (MINI) indicates BPI, BPII, or BP NOS 3. Willing to give consent	1. Dementia 2. Intellectual disability (IQ < 70) 3. Language barrier 4. Poor cognitive functioning (measured by Mini Mental State Examination; MMSE < 18) 5. Insufficiently stable psychiatric condition
GERI-SAD	1. Age > 60 Years 2. BP Disorder-I or II: Depressive episode (DSM-IV-TR; SCID-I/P)	1. Chronic psychotic conditions, ie. schizophrenia, schizoaffective disorder, delusional disorder

(Continued)

SUPPLEMENTAL TABLE 2 (*Continued*)

Individual Study Inclusion and Exclusion Criteria

STUDY NICKNAME	INCLUSION CRITERIA	EXCLUSION CRITERIA
	3. HAM-D > 18 (GRID-HAM-D 24-item version); 4. Availability of an informant is encouraged but not required for study participation.	2. Contraindication to lamotrigine (Physician interview, medical assessment) 3. Documented history of intolerance to lamotrigine 4. Patients who have previously failed to respond to at least 12 weeks of treatment with lamotrigine 5. Active substance dependence (SCID-I/P) or substance-related safety issues or PI concerns 6. Mood Disorder Due to a General Medical Condition or Treatment (Physician interview) 7. Rapid cycling (Physician interview): As defined in DSM-IV: At least 4 episodes of mood disturbance in the previous 12 months that meet criteria for a Major Depressive, Manic, Mixed or Hypomanic Episode. Episodes are distinguished either by partial or full remission for at least 2 months or by a switch to an episode of opposite polarity 8. Dementia (by DSM-IV or brain degenerative diseases; Physician interview) 9. Inability to communicate in English (i.e., interview cannot be conducted without an interpreter; subject largely unable to understand questions and cannot respond in English) 10. Clinically significant sensory impairment (i.e., cannot see well enough to read consent or visually-presented material; cannot hear well enough to cooperate with interview; Physician interview) 11. Recent history of cardiovascular, peripheral vascular events or stroke

(Continued)

SUPPLEMENTAL TABLE 2 (*Continued*)

Individual Study Inclusion and Exclusion Criteria

STUDY NICKNAME	INCLUSION CRITERIA	EXCLUSION CRITERIA
		12. High risk for suicide (e.g., active SI or current intent or plan) 13. Inpatient status.
Inflammaging	1. Diagnosis of Bipolar I or II Disorder by DSM-IV criteria 2. Age 25–60 years, currently outpatient, proficient in English 3. Capable of providing informed consent.	1. Acute medical illness (e.g., cold, flu, bacterial infection, heart failure, cancer) or pregnancy 2. Recent (< 6 weeks) vaccination 3. History of neurological disorder (e.g., dementia, seizures, Parkinson's, stroke) or head trauma with unconsciousness > 15 minutes 4. Diagnosis of substance abuse within the last 3 months or dependence within the last 6 months 5. History of radiation or chemotherapy treatment, uncontrolled diabetes or hypertension, sensory limitations including vision uncorrectable to 20/40, conservatorized, color blindness or hearing loss that interferes with assessment, chronic pain that necessitates treatment with nonsteroidal anti-inflammatory drugs or prescription painkillers that would affect blood-based markers of inflammation.
McGLIDICS	1. Current or past exposure to lithium	1. No exclusion criteria
OABD	Patient group: 1. Older adults (60 years or more) with major affective disorders, i.e. late-life bipolar disorders; or geriatric depression; Comparison groups: 1. Minor Neurocognitive Disorder (DSM-V) or equivalent diagnosis of MCI according to Mayo Clinic criteria; these subjects will be subdivided according to their profile of cognitive deficits	1. Illiteracy 2. Diagnosis of other major DSM-IV Axis I disorders 3. Presence of any acute or major unstable medical illness or organic brain syndromes including dementia (other than AD) 4. Current use of medications to treat medical comorbidities that could possibly affect biological outcome variables (such as non-steroidal anti-inflammatories, insulin or other anti-diabetic drugs)

(Continued)

SUPPLEMENTAL TABLE 2 (*Continued*)

Individual Study Inclusion and Exclusion Criteria

STUDY NICKNAME	INCLUSION CRITERIA	EXCLUSION CRITERIA
	(amnestic; non-amnestic MCI) and the identification of the 'AD-signature' in the CSF as indicated by the concentrations of AD-related biomarkers (low amyloid-beta and high total Tau and phospho-Tau) 2. Major Neurocognitive Disorder due to AD (DSM-V), sub-grouped according to the age of onset of dementia (i.e., early- or late-onset AD) Healthy older adults with normal cognitive function (controls).	Withdrawal or refusal to sign the informed consent (previously approved by the local ethics committee).
OPT-BD	1. Subjects must have type I Bipolar disorder by DSM-IV criteria confirmed on the Mini Neuropsychiatric Interview (MINI) 2. Subjects must be age 60 or older 3. Subjects must have sub-optimal response to current psychotropic management including at least one of the following: a. Behaviors and symptoms of irritability, agitation, mood lability or diminished ability to interact with others in their place of residence 4. Diminished ability to take care of basic personal needs in their place of residence due to symptoms of BD	1. History of intolerance or resistance to asenapine 2. Clinical diagnosis of dementia or Mini-mental state (MMSE) < 24 3. History of TIA, stroke or MI within the past 12 months 4. Medical illness that is the clear, underlying etiology of BD 5. Unstable medical illness or condition including prolonged QT interval, which in the opinion of the study investigators, is likely to affect the outcome of the study or the subject's safety 6. DSM-IV substance dependence (except nicotine or caffeine) within the past 3 months. 7. Rapid cycling BD defined as 4 or more discrete mood episodes within the previous 12 months. 8. At high risk for self-harm or suicide
TMU 2	1. Age 60 years and over 2. Having a final diagnosis of DSM-IV bipolar I disorder 3. Having at least one psychiatric admission to TCPC or TMUH before the start of the study.	1. Patients with comorbid dementia due to other general medical conditions, neurological diseases, and active substance abuse were excluded 2. Must have achieved symptomatic remission prior to study start.

(Continued)

SUPPLEMENTAL TABLE 2 (*Continued*)

Individual Study Inclusion and Exclusion Criteria

STUDY NICKNAME	INCLUSION CRITERIA	EXCLUSION CRITERIA
UBBDPC	1. Being aged 18 or older 2. Presenting a diagnosis of bipolar disorder following DSM-IV-TR criteria 3. Being outpatient at the moment of the assessment	1. History of intellectual disability 2. Any medical condition that could interfere in the assessment procedure
UPMC	1. Age ⩾ 50 years 2. Clinical euthymia for four weeks preceding neurocognitive assessment with scores of ⩾ 10 on both the 17-item Hamilton Rating Scale for Depression (HRSD) (46) and the Young Mania Rating Scale (YMRS) (47) at the time of assessment 3. Ability to comprehend and speak English fluently 4. Corrected visual ability to read newspaper headlines 5. Hearing capacity adequate to respond to a raised conversational voice	1. History of dementia or neurologic disorder affecting the central nervous system (e.g., Parkinson's disease, traumatic brain injury, or multiple sclerosis) 2. Electroconvulsive therapy within the past six months 3. Substance abuse or dependence within the past 12 months. 4. For this report, we focused on subjects who had completed both neuroimaging and neurocognitive assessment.
Yale	1. BP 1 or 2 2. No contraindications to MRI scanning 3. No recent substance abuse/ dependence	1. Recent substance abuse or dependence 2. Contraindications to magnetic resonance imaging (MRI) 3. Intellectual disability (intelligence quotient < 70) 4. Pregnancy 5. Significant or unstable medical illness that could affect the brain e.g., insulin dependent diabetes 6. Neurological illness that could have effects on the brain 7. History of loss of consciousness for 5 or more minutes
ZIP-AD	1. Diagnosis of Type I or II BD for at least 6 months (confirmed with MINI) 2. On maintenance evidence-based treatment for BD (lithium, antipsychotic, anticonvulsant)	1. Known resistance or intolerance to ziprasidone. 2. Medical contraindication to ziprasidone. 3. Individuals on ziprasidone immediately prior to study enrollment.

(Continued)

SUPPLEMENTAL TABLE 2 (*Continued*)

Individual Study Inclusion and Exclusion Criteria

STUDY NICKNAME	INCLUSION CRITERIA	EXCLUSION CRITERIA
	3. Have weight gain concerns that individual believes are related to BD medication treatment. 4. Sub-optimal adherence as measured by the Tablet Routines Questionnaire (TRQ) and which the patient feels is related to weight gain concerns. TRQ threshold will be defined as missing 20% or more of prescribed BD treatment in last week or last month. This is consistent with methodologies in PIs previous BD adherence studies.	4. Prior or current treatment with clozapine. 5. Diagnosis of eating disorder 6. Individuals whose sub-optimal adherence is related to inability to pay for BD medication treatment or inability to arrange transportation to BD treatment clinical visits 7. Concurrent medical condition or psychiatric illness, which in the opinion of the research psychiatrist, would interfere with the patient's ability to participate in the trial. 8. Current substance dependence. 9. High risk of harm to self or others. 10. Female who is currently pregnant or breastfeeding.