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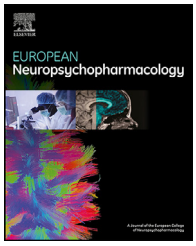

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Comparative analysis of anticholinergic burden scales to explain iatrogenic cognitive impairment and self-reported side effects in the euthymic phase of bipolar disorders: Results from the FACE-BD cohort

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Abstract
Bipolar disorders (BD) are characterized by cognitive impairment during the euthymic phase, to which treatments can contribute. The anticholinergic properties of medications, i.e., the ability of a treatment to inhibit cholinergic receptors, are associated with cognitive impairment in elderly patients and people with schizophrenia but this association has not been well characterized in individuals with remitted BD. Moreover, the validity of only one anticholinergic burden scale designed to assess the anticholinergic load of medications has been tested in BD. In a literature review, we identified 31 existing scales. We first measured the associations between 27 out of the 31 scales and objective cognitive impairment in bivariable regressions. We then adjusted the bivariable models with covariates: the scales significantly associated with cognitive impairment in bivariable and multiple logistic regressions were defined as having good concurrent validity to assess cognitive impairment. In a sample of 2,031 individuals with euthymic BD evaluated with a neuropsychological battery, two scales had good concurrent validity to assess cognitive impairment, whereas chlorpromazine equivalents, lorazepam equivalents, the number of antipsychotics, or the number of treatments had not. Finally, similar analyses with subjective anticholinergic side-effects as outcome variables reported 14 scales with good concurrent validity to assess self-reported peripheral anticholinergic side-effects and 13 to assess self-reported central anticholinergic side-effects. Thus, we identified valid scales to monitor

the anticholinergic burden in BD, which may be useful in estimating iatrogenic cognitive impairment in studies investigating cognition in BD.

1. Introduction

Type I and II bipolar disorders (BD) affect 1.06 and 1.57% of the population, respectively (Clemente et al., 2015) and can be associated with cognitive impairment in all phases of the illness (Cipriani et al., 2017). During manic and depressive episodes, bipolar patients show globally impaired verbal memory, language, attention, and executive functions (Cipriani et al., 2017; Ha et al., 2014; Kurtz and Gerraty, 2009). In the euthymic phase, patients also show impairment in all cognitive domains in 12.4 to 39.7% of cases (Bora et al., 2016; Burdick et al., 2014; Jensen et al., 2016; Roux et al., 2019). In BD, impaired cognition is associated with more frequent affective episodes (Sánchez-Morla et al., 2019), lower quality of life (Cotrena et al., 2016), and impaired social functioning (Baune and Malhi, 2015). The current management of BD largely involves pharmacological interventions. In addition, in 2016 between 7% and 10% of German medicated patients exhibited a clinically relevant anticholinergic burden (Reinold et al., 2021). Yet, the cognitive effects of medication in BD have been under-investigated. Psychotropic drugs are generally associated with cognitive improvement when they treat affective episodes (Kurtz and Gerraty, 2009) but may be associated with residual cognitive impairment during the euthymic period (Bourne et al., 2013; Roux et al., 2019; Xu et al., 2020). Anticholinergic properties of the treatment, which refer to its inhibitory activity on acetylcholine receptors, have been suspected of contributing to iatrogenic effects on cognition in healthy subjects (Mintzer and Griffiths, 2003). Such findings led to the design of anticholinergic burden scales to quantify the cumulative anticholinergic burden of treatment (Al Rihani et al., 2021). The association between the scores of such scales and cognitive impairment has been largely studied in populations with cognitive frailty, such as the elderly and individuals with schizophrenia (Lisibach et al., 2021; Georgiou et al., 2021), whereas it has only been characterized once in BD (Eum et al., 2017). Eum et al. reported the absence of a significant association between the Anticholinergic Drug Scale (ADS; Carnahan et al., 2006) and the composite score on a brief cognitive battery for 146 clinically stable patients with BD and psychotic features. The concurrent validity of other scales to evaluate cognitive impairment has never been tested in BD, despite large discrepancies between existing scales that are mainly due to the different methods used to design them (Rudd et al., 2005). For example, some scales were designed based exclusively on in vitro objective measures of serum anticholinergic activity of the drugs (Chew et al., 2008), whereas others were designed based on a literature review of the anticholinergic properties of the drugs discussed by experts (Rudolph et al., 2008). In addition, the same drug can be classified as highly anticholinergic by one scale and not anticholinergic by another: perphenazine is highly anticholinergic on the Anticholinergic Risk Scale (Rudolph et al., 2008) but is not anticholinergic on Chew's scale (Chew et al., 2008). Although most recent scores are more convergent than older ones (Al Rihani et al., 2021), the considerable differences between scales argue for the need to identify the most optimal tools to assess the anticholinergic cognitive burden, specifically in BD. Our primary objective was to assess the associations between existing scales and cognitive impairment in individuals with BD and subsequently identify valid scales capable of identifying individuals at the highest risk of iatrogenic cognitive impairment. To achieve this, we performed multiple logistic regressions while adjusting for relevant covariates to establish the concurrent validity of the identified scales in assessing cognitive impairment. Next, we conducted ROC curve analyses to determine the sensitivity and specificity of each scale in accurately diagnosing cognitive impairment in the context of BD. Based on our findings, our ultimate objective was to recommend an appropriate scale to effectively identify individuals with BD at a higher risk of cognitive impairment in clinical settings. In addition to the cognitive burden, anticholinergic burden scales should monitor other anticholinergic side effects. Thus, this study also aimed to identify the scales with the best concurrent validity against common peripheral (such as dry mouth, constipation, and blurred vision) and central anticholinergic side effects (such as drowsiness and confusion) reported by individuals with BD. As with cognitive impairment, the scales associated with common anticholinergic side effects in multiple regressions were identified as having good concurrent validity in BD.

2. Experimental procedures

The preregistration of the article is available at https://osf.io/zsrph/?view_only=753ecc167870464a8d88e0cd654e5085.

2.1. Study design and characteristics of the recruiting network

This multicenter transversal study included patients recruited into the FACE-BD (FondaMental Advanced Centers of Expertise for Bipolar Disorders) cohort within a French national network of 10 centers (Bordeaux, Colombes, Créteil, Grenoble, Marseille, Monaco, Montpellier, Nancy, Paris, and Versailles). This network was created by the Fondation FondaMental (https://www.fondation-fondamental.org), which organized and provided the necessary resources to follow cohorts of patients with BD, promoting comparative research. The local ethics committee approved the study (Comité de Protection des Personnes Ile-de France IX) on January 18, 2010, under French law for non-interventional studies (observational studies without any risk, constraint, supplementary or unusual procedure concerning diagnosis, treatment, or monitoring). The board required that all patients be given an informational letter but waived the requirement for written informed consent. However, verbal consent was witnessed and formally recorded.

2.2. Participants

The diagnosis of BD was based on the Structured Clinical Interview for DSM-IV-TR (SCID) criteria (First et al., 1997). Outpatients between 18 and 65 years of age with type I, II, or not otherwise specified (NOS) BD were eligible for the present study. We selected patients who were euthymic at the time of testing according to the DSM-IV-R criteria and who had scores on the Montgomery Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979) $\leq$ 10 and the Young Mania Rating Scale (YMRS; Young et al., 1978) $\leq$ 12. We excluded non-euthymic participants, as previous studies reported that mood symptoms may influence cognitive performance (Kurtz and Gerraty, 2009) and self-reported side effects (Gao et al., 2008; Vaccarino et al., 2009) beyond the iatrogenic load.

We also excluded patients with a history of neurological disorders, dyslexia, dyscalculia, dysphasia, dysorthographia, dyspraxia, any episode of substance abuse disorder in the previous months, or electro-convulsive therapy in the past year, again to remove other sources of cognitive impairment other than medications.

2.3. Measures

2.3.1. Anticholinergic burden scales

We searched for existing anticholinergic burden scales by conducting a literature review on Google Scholar, PubMed, and Cochrane in November 2022 (see Supplementary Information for more details). We identified 36 scales, and excluded seven because they excluded psychotropic medications, did not provide a score, or did not evaluate exclusively anticholinergic properties. Besides, we favored and included the most recent version of each scale: the lists of the excluded and included scales are reported in Supplementary Information.

Drugs not included in a scale were scored 0, as if they had no anticholinergic properties according to the scale, as in a previous study (Lisibach et al., 2022a). Two methods to compute the total anticholinergic burden of the treatment were used: summing the scores ("sum"), as recommended by Carnahan et al. (2006), and using the highest score ("max"), as recommended by Sittironnarit et al. (2011).

2.3.2. Cognition

Experienced neuropsychologists administered the tests in a fixed order that was the same for every center. Testing lasted approximately 120 min, including 5-to-10-min breaks. The standardized test battery complied with the recommendations of the International Society for Bipolar Disorders (Yatham et al., 2010) and included 11 tests, including five subtests from the Wechsler Adult Intelligence Scale version III (WAIS III) (Wechsler, 1997a) or version IV (Wechsler et al., 2008), as the French version of the WAIS-IV started to be used in the FACE-BD cohort as it became available. The battery evaluated six domains:

- Processing speed: Digit symbol coding (WAIS-III) or coding (WAIS-IV), WAIS symbol search, and Trail Making Test, part A (Reitan, 1958)
- Verbal memory: California Verbal Learning Test short and long delay-free recall and total recognition (Delis, 2000)
- Attention: Conners' Continuous Performance Test II V.5 (omission, commission, variability, and detectability) (Conners and Staff, 2000)
- Working memory: WAIS digit span (total score) and spatial span (forward and backward scores) from the Wechsler Memory Scale version III (Wechsler, 1997b)
- Executive function: color/word condition of the Stroop test (Golden, 1978), semantic and phonemic verbal fluency (Lezak, 2004), and Trail Making Test, part B (Reitan, 1958)
- Verbal and perceptual reasoning: WAIS vocabulary and matrices

Higher scores reflect better performance. We converted the raw scores of each test to standardized scores based on normative data (Conners and Staff, 2000; Godefroy, 2008; Golden, 1978; Poitrenaud et al., 2007). We computed a global deficit score or GDS (Heaton et al., 2004) to determine a threshold for cognitive impairment (see Supplementary information for details about the computation method). We also computed a mean z-score for each cognitive domain.

2.3.3. Drug side effects

Adverse effects were assessed using the Patient-Rated Inventory of Side Effects Modified (PRISE-M; Rush et al., 2004; Rush and O'Neal, 1999). The PRISE-M evaluates the tolerance level for 32 side effects in nine domains (gastro-intestinal, cardiovascular, skin, nervous, sensory systems, urogenital systems, sleep, sexual function, and others). Each item was coded 0 for absent, 1 for bearable, and 2 for painful. We computed two scores for anticholinergic side effects based on the usual anticholinergic side effects reported in the literature (Feinberg, 1993; Fond et al., 2019; Giuliano and Droupy, 2013; Lieberman, 2004). The peripheral score was the sum of the following item scores: "dry mouth", "constipation", "blurred vision", "dry skin", "itching", "difficulty urinating", "frequent urination", "erectile dysfunction", and "orgasm disorders". The central score was the sum of the scores of "increased sleep time", "loss of energy", "asthenia", "impaired concentration", "general malaise", "reduced sex drive", and "orgasm disorders".

2.3.4. Clinical covariates and alternative measures of iatrogenic cognitive burden

Socio-demographic (sex, age, education level) and clinical variables, such as the age at onset of BD, the total number of mood episodes, the subtype of BD, and a history of psychotic symptoms were recorded. Mania was evaluated by the Young Mania Rating Scale (YMRS), depression by the Montgomery Asberg Depression Rating Scale (MADRS), and symptoms severity by the Clinical Global Impressions scale (CGI; Guy, 1976). We also recorded the class of treatment (antidepressants, anticonvulsants, lithium, antipsychotics, anxiolytics, and antiparkinsonian drugs prescribed for extrapyramidal side effects). These variables were all screened as potential covariates of the association of anticholinergic load with cognitive deficit, as well as with peripheral and central anticholinergic side effects. We additionally recorded whether a patient used multiple classes of treatment, i.e., two or more different classes, for information.

We collected alternative measures associated with iatrogenic cognitive burden: the number of medications (reported in Dias et al., 2012), the number of antipsychotics (reported in Bourne et al., 2013), chlorpromazine (reported in Jamrozinski et al., 2009) equivalents (CPZeq, computed from the formulas proposed by Andreasen et al., 2010 and Leucht et al., 2015), and lorazepam (reported in Savić et al., 2021) equivalents (computed from the formulas proposed by Kane, 2017). As for the anticholinergic burden scales, we assessed whether these measures were associated with cognitive impairment.

2.4. Statistical analysis

Statistical analyses were carried out using R. For the multiple analyses, we estimated that data of the covariates were Missing At Random (MAR) and were thus estimated using multivariate imputation by chained equations (50 imputations, *mice* package of R, Van buuren and Groothuis-Oeudshoorn, 2011). Each variable had $<$ 30% missing data, allowing the use of multiple imputations (Marshall et al., 2010). We compared imputed and non-imputed datasets to ensure the validity of the imputed values (Nguyen et al.,

Table 1 Description of the sample ($n = 2031$).

Category	*n*	*Mean (SD)*	*% missing data*
Female, n (%)	1254 (62%)		1%
Age (mean, ±SD)		39.6 (12.3)	0%
Education level (years)		14.4 (2.6)	6%
Cognitive impairment, n (%)	393 (19%)		15%
MADRS (mean, ±SD)		4.13 (3.22)	4%
YMRS (mean, ±SD)		1.70 (2.65)	4%
CGI (mean, ±SD)		2.6 (1.4)	6%
Type I BD, n (%)	1050 (52%)		0%
Type II BD, n (%)	790 (39%)		0%
Unspecified BD, n (%)	191 (9%)		0%
End of the last characterized mood episode > 3 months before, n (%)	1589 (78%)		10%
Age at the first mood episode (mean, ±SD)		23.9 (9.2)	10%
Number of depressive episodes (mean, ±SD)		5.4 (6.4)	20%
Number of manic episodes (mean, ±SD)		1.2 (2.1)	7%
Number of hypomanic episodes (mean, ±SD)		3.4 (6.1)	29%
Number of mixed episodes (mean, ±SD)		0.4 (1.5)	22%
Patients with history of psychosis, n (%)	724 (36%)		18%

MADRS: Montgomery-Asberg Depression Rating Scale.
YMRS: Young Mania Rating Scale.
CGI: Clinical Global Impressions scale.

2017). The fraction of missing information (fmi) computed by the *pool* function of the *mice* package is reported in the results.

First, we assessed the associations between the 27 anticholinergic scale scores and the presence of a cognitive deficit using successive bivariable logistic regressions.

For scales associated with a cognitive deficit at a 0.05 significance level in bivariable analyses, we ran successive multiple logistic regressions of the scores on the presence of a cognitive deficit that included a subset of covariates. Covariates were included in the model if they were associated with the scale validated by the most studies, i.e., the Anticholinergic Cognitive Burden scale (Boustani et al., 2008; Lisibach et al., 2021), with a p-value < 0.2, as pre-established in the preregistration. We also ran multiple logistic regression analyses using the four alternative measures of iatrogenic cognitive burden (number of medications, number of antipsychotics, chlorpromazine equivalents, and lorazepam equivalents) with the same set of covariates.

We then conducted receiver operating characteristic (ROC) curve analysis for scales associated with cognitive impairment in the multiple analysis at a 0.05 significance level. The area under the curve (AUC) was interpreted as follows: 0.5: unpredictive, 0.5–0.7: poorly predictive, 0.7–0.9: moderately predictive, > 0.9: strongly predictive.

We also assessed the associations between the scales and peripheral and central anticholinergic side-effects scores using the same analytical framework as above using linear regressions.

Finally, we computed the correlations (Spearman rho) between the scales significantly associated with peripheral or central anticholinergic side-effect subscores in multiple regression models and each item of the PRISE-M to explore which self-reported side effects were associated with the scales and whether the scales were sensitive to non-anticholinergic adverse effects. We applied the false-discovery procedure of Benjamini-Hochberg to p-values, with the significance level set to 0.05 (Benjamini and Hochberg, 1995).

3. Results

3.1. Description of the sample

We included 2031 participants with euthymic bipolar disorders (62% female), among whom 393 (19%) were considered to be cognitively impaired by the GDS criterion (Table 1). The characteristics of the treatments are presented in Table 2. The anticholinergic scales reported between 1.13%

Table 2 Characteristics of the treatments ($n = 2031$).

Variable	*n*	*Mean (SD)*	*% missing data*
Number of medications		2 (1)	30%
Number of antipsychotics		0.5 (0.6)	30%
Number of patients using antidepressants, n (%)	492 (34%)		30%
Number of patients using anticonvulsant, n (%)	702 (49%)		30%
Number of patients using lithium, n (%)	507 (36%)		30%
Number of patients using antipsychotic, n (%)	617 (43%)		30%
Number of patients using anxiolytic, n (%)	344 (24%)		30%
Number of patients using antiparkinsonian drug, n (%)	22 (2%)		30%
Number of patients using multiple classes, n (%)	456 (32%)		30%
Chlorpromazine equivalent, mg/24 h (mean, ±SD)		103.6 (183.8)	31%
Lorazepam equivalent, mg/24 h (mean, ±SD)		0.11 (0.58)	30%

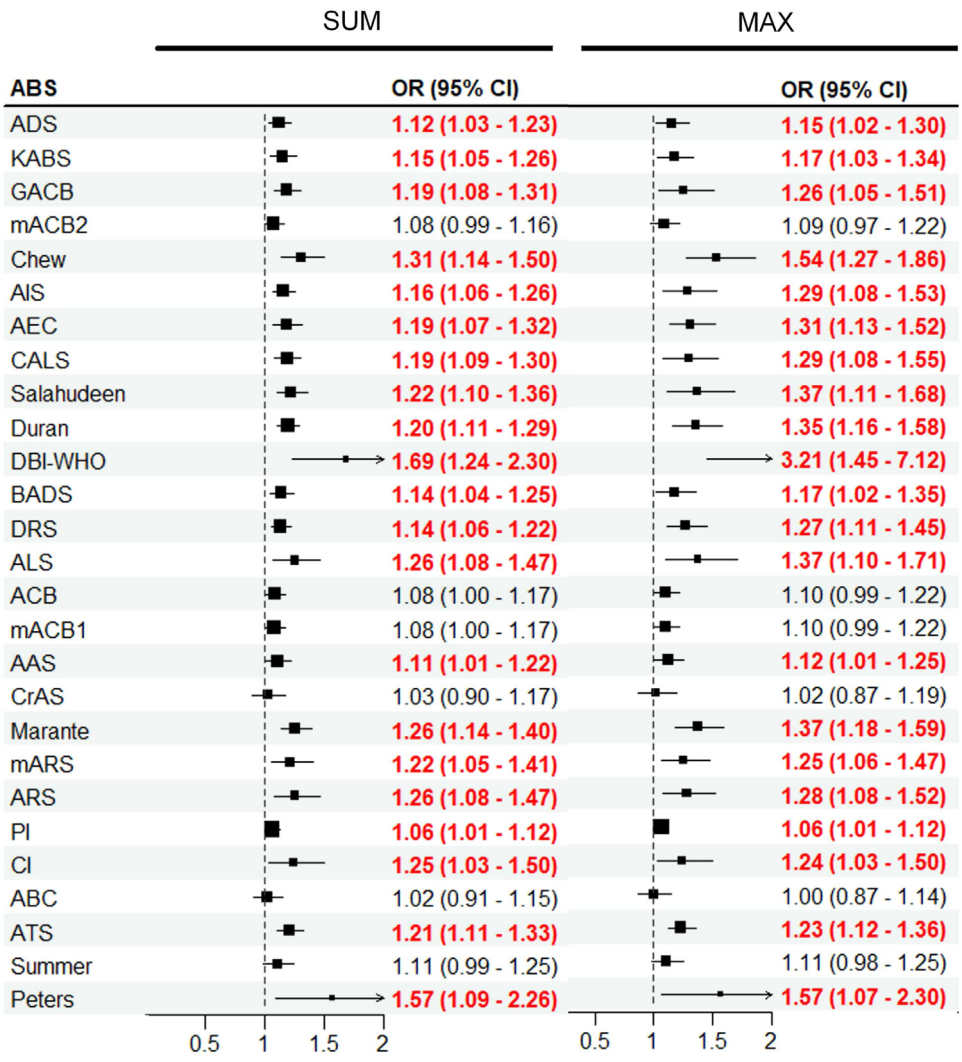

Fig. 1 Results of the bivariable logistic regression models of cognitive impairment with the scales as the predictor. Significant ($p < 0.05$) odds ratios are shown in red. The total anticholinergic burden score was computed by either summing the scores of each treatment (SUM) or by using the maximum score (MAX).

and 67.01% patients with a non-zero score, i.e., with an anticholinergic burden, indicating a large discrepancy between scales (Supplementary Fig. 2).

3.2. Cognitive impairment and anticholinergic burden scales

The bivariable regressions of cognitive impairment, defined by the GDS criterion, on the anticholinergic burden scales are reported in Fig. 1. The values of 21 scales were significantly positively associated with cognitive impairment when using the "sum" method ($1.06 \leq \text{OR} \leq 1.69$) and the "max" method ($1.06 \leq \text{OR} \leq 3.21$). We then adjusted the bivariable models of the 21 scales with a set of covariates (see the covariate selection process in Supplementary Information). The values from two of the 21 scales were significantly associated with cognitive impairment after the inclusion of the covariates: Chew's scale (Chew et al., 2008), computed using the "max" method, and the Anticholinergic Toxicity Scale (ATS; Xu et al., 2017), computed using the "sum" and "max" methods (Table 3, see Supplementary Table 2 for the results of the other 21 scales). An increase of 1 point in the maximum Chew's score or the Anticholinergic Toxicity Scale was associated with a 33% or 11 to 14% increase, respectively, of the odds of being cognitively impaired. Chew's scale was also significantly associated with cognitive impairment in a sensitivity analysis run on the dataset with complete cases, unlike the Anticholinergic Toxicity Scale (Supplementary Table 3). The number of medications, antipsychotics, CPZeq, and lorazepam equivalents were not significantly associated with cognitive impairment after adjusting on the same set of covariates (Supplementary Table 4). Among the covariates, the use of lithium was significantly associated with more frequent cognitive impairment ($1.62 \leq \text{OR} \leq 1.98$), and education level was significantly associated with less frequent cognitive impairment ($\text{OR} = 0.87$) in all multiple regression models. The use of antipsychotics and antiparkinsonian drugs was significantly associated with more frequent cognitive impairment in 96% and 52% of the

Table 3 Multiple logistic regression models of cognitive impairment with a significant association between the scale and cognitive impairment. The total anticholinergic burden score was computed by either summing the scores of each treatment (sum) or by using the maximum score (max). Significant associations are in bold. The covariates included in the models were: MADRS score, history of psychosis, the use of antidepressants, lithium, antipsychotics, anxiolytics, or antiparkinsonian drugs, the number of previous depressive and manic episodes, age at the first thymic episode, CGI score, and the education level. ATS: Anticholinergic Toxicity Scale (Xu et al., 2017), Chew: Chew's scale (Chew et al., 2008), fmi: fraction of missing information.

	Chew (max)			ATS (sum)			ATS (max)		
	OR (95% CI)	p-value	fmi	OR (95% CI)	p-value	fmi	OR (95% CI)	p-value	fmi
Scale	**1.33 (1.06 - 1.67)**	**0.013**	0.12	**1.11 (1.01 - 1.23)**	**0.039**	0.14	**1.13 (1.01 - 1.27)**	**0.027**	0.20
MADRS	0.98 (0.94 - 1.03)	0.41	0.12	0.98 (0.94 - 1.02)	0.35	0.07	0.98 (0.93 - 1.02)	0.291	0.12
History of psychosis	0.93 (0.67 - 1.29)	0.673	0.21	0.9 (0.64 - 1.28)	0.562	0.30	0.91 (0.65 - 1.26)	0.567	0.21
Antidepressants	0.76 (0.54 - 1.05)	0.095	0.15	0.82 (0.6 - 1.12)	0.21	0.14	0.83 (0.61 - 1.14)	0.25	0.16
Lithium	**1.66 (1.21 - 2.29)**	**0.002**	0.16	**1.88 (1.4 - 2.51)**	**<0.001**	0.15	**1.93 (1.44 - 2.59)**	**<0.001**	0.14
Antipsychotics	**1.51 (1.11 - 2.04)**	**0.008**	0.13	**1.55 (1.15 - 2.07)**	**0.004**	0.10	**1.56 (1.16 - 2.09)**	**0.003**	0.11
Anxiolytics	1.26 (0.9 - 1.74)	0.176	0.18	1.21 (0.87 - 1.68)	0.249	0.15	1.22 (0.88 - 1.69)	0.24	0.18
Antiparkinsonian	**2.67 (1.05 - 6.79)**	**0.039**	0.06	2.11 (0.8 - 5.56)	0.131	0.07	2.19 (0.85 - 5.67)	0.105	0.07
Education level	**0.87 (0.82 - 0.91)**	**<0.001**	0.12	**0.87 (0.82 - 0.91)**	**<0.001**	0.13	**0.86 (0.82 - 0.91)**	**<0.001**	0.12
Age at first episode	1 (0.99 - 1.02)	0.808	0.28	1 (0.99 - 1.02)	0.641	0.22	1 (0.99 - 1.02)	0.775	0.29
Number of manic episode	1.06 (0.99 - 1.14)	0.086	0.21	1.07 (0.99 - 1.14)	0.082	0.23	1.06 (0.99 - 1.14)	0.086	0.21
Number of depressive episode	1 (0.98 - 1.03)	0.757	0.27	1 (0.98 - 1.03)	0.85	0.34	1 (0.98 - 1.03)	0.832	0.28
CGI	1.1 (0.99 - 1.21)	0.065	0.16	1.09 (0.99 - 1.21)	0.093	0.21	1.1 (0.99 - 1.21)	0.071	0.17

multiple regression models, respectively ($1.47 \leq OR \leq 1.68$ and $2.58 \leq OR \leq 2.78$, respectively). The AUC for Chew's scale and the Anticholinergic Toxicity Scale was 0.57 and 0.53, respectively (Fig. 2), thus suggesting poor predictability ($0.5 < AUC < 0.7$) of cognitive impairment by the two scales at an individual level.

Besides, we ran complementary analyses to explore which scale would be the most useful in order to adjust medication when a cognitive deficit is identified with a neuropsychological battery. We conducted multiple linear regression models of the z-score in the six cognitive domains (processing speed, verbal memory, attention, working memory, executive function, and reasoning) and the 27 scales in the subsample identified as cognitively impaired by the GDS criteria ($n = 393$), with the same set of covariates as in previous analyses. We reported the standardized coefficient of each scale estimated by the model (Supplementary Fig. 3). Chew's scale (computed by the sum or max method) exhibited a significant association with poorer reasoning and processing speed performances and was the only scale significantly associated with more than one cognitive domain. In addition, the Pharmacological Index (computed by the sum or max method) was significantly associated with poorer processing speed. Finally, Summers's scale was significantly associated with improved executive function. The direction of the latter association could be explained by the fact that Summers's scale has limited coverage, as suggested by Supplementary Fig. 2: in fact, 70% of the 393 individuals had a Summers score of zero. This limited coverage could have introduced bias in the estimation of the association between Summers' score and cognitive performance in the subsample of people with cognitive impairment.

3.3. Self-reported side effects and anticholinergic burden scales

Among the 27 scales, 21 were significantly associated with the subscore for peripheral anticholinergic side effects (Standardized β: $0.055 \leq \beta \leq 0.158$; $0.003 \leq R^2 \leq 0.025$), and 22 were significantly associated with the subscore for central anticholinergic side effects (Standardized β: $0.058 \leq \beta \leq 0.190$; $0.003 \leq R^2 \leq 0.036$) in bivariable logistic regression models (Supplementary Fig. 4). We then adjusted the 21 models for the peripheral subscore and the 22 for the central subscore with the same set of previously selected covariates. Fourteen scales were significantly associated with the peripheral subscore in multiple logistic regression models when using the "max" method, the "sum" method, or both (Standardized β: $0.032 \leq \beta \leq 0.157$; $0.09 \leq R^2 \leq 0.10$) (Supplementary Table 5): the Anticholinergic Burden Classification (Ancelin et al., 2006), the Anticholinergic Risk Scale (Rudolph et al., 2008), the Anticholinergic Cognitive Burden scale (Boustani et al., 2008), the Anticholinergic Impregnation Scale (Briet et al., 2017), the Brazilian Anticholinergic Activity Drug Scale (Nery and Reis, 2019), the CRIDECO Anticholinergic Load Scale (Ramos et al., 2022), the Delirogenic Risk Scale (Hefner et al., 2015), Durán's scale (Durán et al., 2013), the German Anticholinergic Burden Scale (Kiesel et al., 2018), the Korean Anticholinergic Burden Scale (Jun et al., 2019), the Muscarinic Acetylcholinergic Receptor ANTagonist Exposure Scale (Klamer et al.,

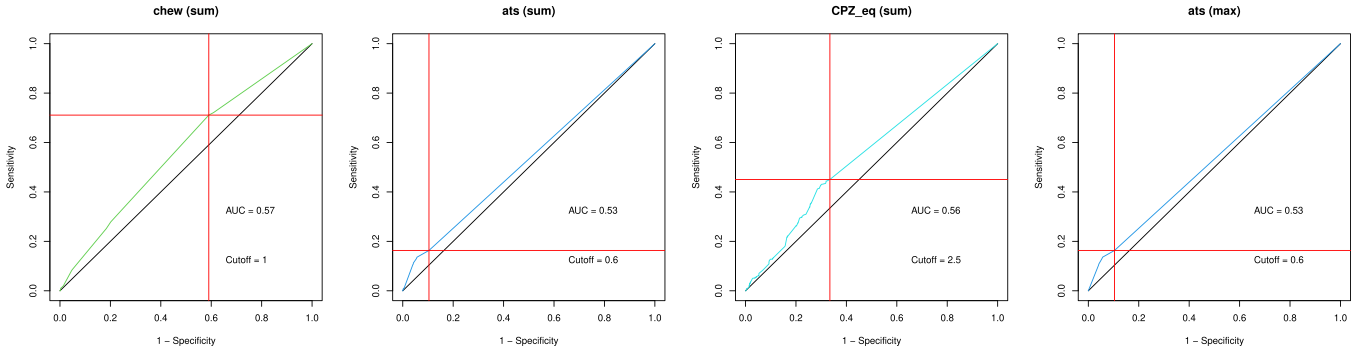

Fig. 2 ROC curves for Chew's scale, the Anticholinergic Toxicity Scale, and chlorpromazine equivalents as classifiers of cognitive impairment. Cutoffs were computed using Unal's guidelines (2017): the cutoff represents the value for which the sensitivity and specificity are the closest to the value of the area under the ROC curve such that the absolute value of the difference between the sensitivity and specificity values is minimum. Red lines indicate the specificity and sensitivity at the cutoff. ats: Anticholinergic Toxicity Scale, AUC: area under the curve, chew: Chew's Scale, CPZ_eq: chlorpromazine equivalents.

2017), the modified Anticholinergic Cognitive Burden Scale of Joshi et al. (2021), the modified Anticholinergic Risk Scale of Sumukadas et al. (2014), and Salahudeen's scale (Salahudeen et al., 2015). Thirteen scales were significantly associated with the central subscore in multiple logistic regression models (Standardized β: $0.039 \leq \beta \leq 0.153$; $0.21 \leq R^2 \leq 0.22$) (Supplementary Table 6) (a list of the 13 scales is available in Supplementary Information). We drew pairwise correlations between the scales significantly associated with the peripheral or the central score in multiple regression analyses and each item of the PRISE-M (see Fig. 3). All scales were significantly associated with an increase in patient-reported dry mouth ($0.08 \leq$ rho ≤ 0.16) and weight gain ($0.08 \leq$ rho ≤ 0.17). More than 12/15 scales were significantly associated with increased sleep time, more constipation, asthenia, loss of energy, and reduced sex drive. Certain scales were also significantly positively associated with side effects not included in the peripheral or central anticholinergic subscores, such as diarrhea, palpitations, tinnitus, tremor, dizziness, vertigo, anxiety, and agitation.

4. Discussion

We tested the concurrent validity of 27 existing anticholinergic scales against cognitive impairment and self-reported anticholinergic side effects of medication in a large sample of individuals with bipolar disorders who were euthymic at the time of testing. We found marked discrepancies in the number of drugs with anticholinergic properties listed in each scale, as reported in a previous study that included 11 (Al Rihani et al., 2021) of the 27 scales used in the present study.

We identified two scales with acceptable concurrent validity to assess cognitive impairment: Chew's scale using the "max" method and the Anticholinergic Toxicity Scale using either the "max" or "sum" method. Chew's scale and the Anticholinergic Toxicity Scale were more robust indicators of cognitive impairment than antipsychotic load measured by chlorpromazine equivalents, which is associated with poorer performance in attention in BD (Jamrozinski et al., 2009). In addition, Chew's scale remained significantly associated with cognitive impairment in complete case analysis, which was not the case for the Anticholinergic Toxicity Scale. We replicated the lack of association between cognitive impairment in bipolar patients and Anticholinergic Drug Scale values reported by Eum et al. (2017). Previous use of Chew's scale showed its association with cognitive impairment in elderly patients (Lampela et al., 2013; Lisibach et al., 2021), whereas the Anticholinergic Toxicity Scale has been shown to be strongly associated with delirium and mortality in elderly patients (Lisibach et al., 2022a & 2022b), but no study has explored their association with cognitive performance for individuals with psychiatric disorders. Indeed, Chew's scale was designed based exclusively on in vitro measures of serum anticholinergic activity, and the Anticholinergic Toxicity Scale was designed based on the affinity for muscarinic receptors deduced from the molecular structure of the drug: neither of the two scales was designed based on clinical observations, making our results quite unexpected. Our results suggest that completely objective scales based on computational or in vitro receptor affinities might be better indicators of cognitive impairment than other scales that account for patients' reports of anticholinergic side effects or expert opinions. In addition, using completely objective scales provides interesting perspectives for research. Indeed, new pharmacological agents could be positioned on the scale from the earliest phases of their development before pharmacovigilance and expert consensus. Besides, according to Chew's scale, lithium, quetiapine, and olanzapine have anticholinergic properties and were frequently prescribed in our sample (Supplementary Table 7). Further studies should thus investigate the cognitive impact of these three candidate medications in BD. Despite significant associations of Chew's scale and the Anticholinergic Toxicity Scale with cognitive impairment, ROC curve analyses showed them to be insufficiently strong to establish a threshold for the risk of iatrogenic cognitive impairment at the individual level, which would be useful in selecting participants for interventional studies targeting cognitive improvement in BD. However, we recommend using these scales in studies that require controlling for the burden of medication on cognition at the group level.

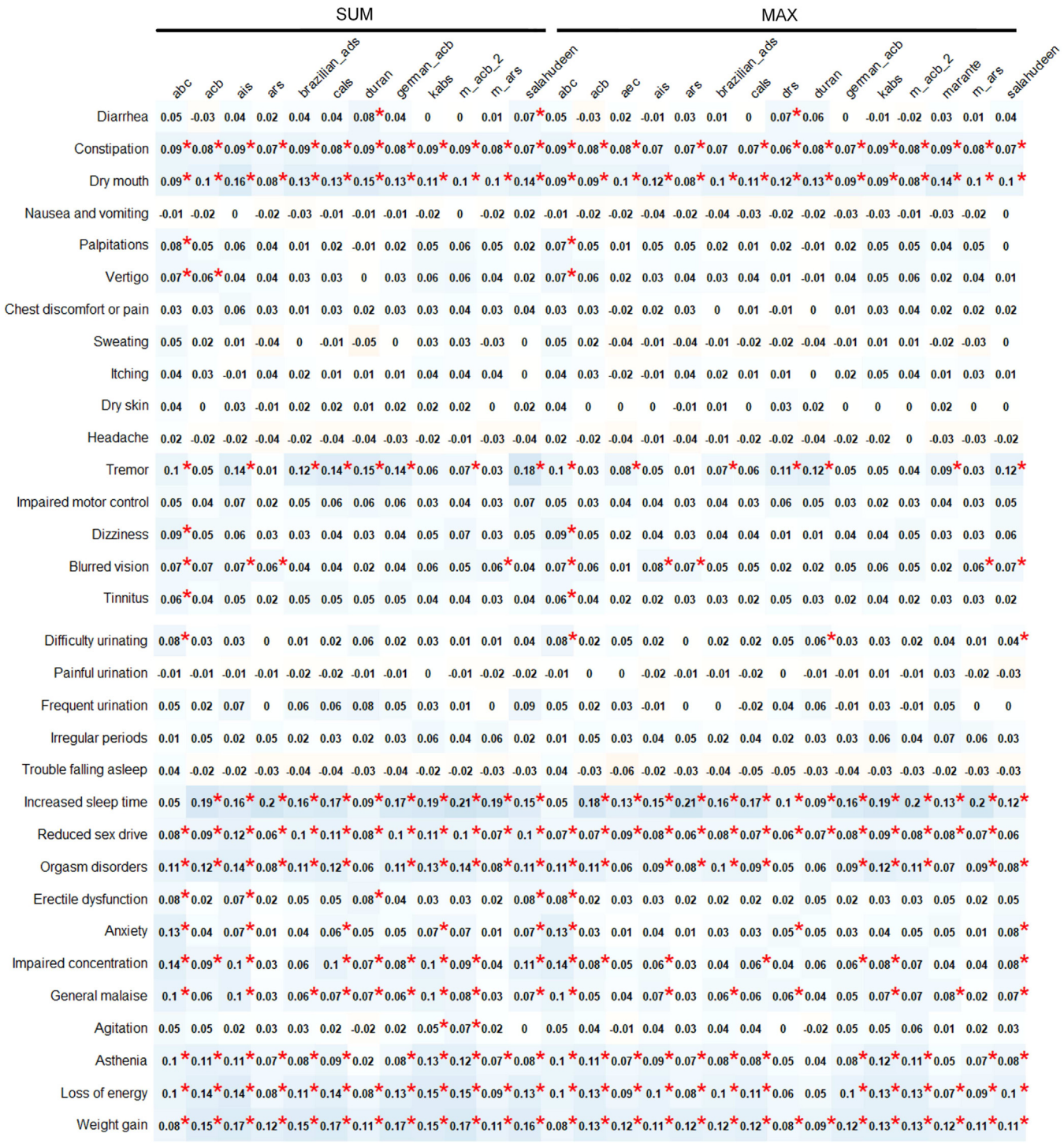

Fig. 3 Pairwise correlations (Spearman rho coefficients) between items of the PRISE-M questionnaire and 15 anticholinergic burden scales. Colors indicate the strength and valence of the correlation. A star indicates significance at the 5% level after Benjamini-Hochberg/false-discovery rate correction. abc: Anticholinergic Burden Classification; acb: Anticholinergic Cognitive Burden Scale; aec: Anticholinergic Effect on Cognition; ais: Anticholinergic Impregnation Scale; ars: Anticholinergic Risk Scale; brazilian_ads: Brazilian Anticholinergic Activity Drug Scale; cals: the CRIDECO Anticholinergic Load Scale; drs: Delirogenic Risk Scale; duran: Durán's Scale; german_acb: German Anticholinergic Burden Scale; kabs: Korean Anticholinergic Burden Scale; m_acb_2: Modified Anticholinergic Cognitive Burden Scale 2; marante: Muscarinic Acetylcholinergic Receptor ANTagonist Exposure Scale; m_ars: Modified Anticholinergic Risk Scale; salahudeen: Salahudeen's Scale.

For individuals with clinically significant cognitive impairment, Chew's scale was significantly associated with worse performance in processing speed and reasoning, albeit weakly. This is the first evidence of an association between anticholinergic burden and processing speed and reasoning in BD. Our results advocate for the use of Chew's scale to help manage treatment in treated euthymic individuals with BD and impaired cognitive functions, especially when processing speed and reasoning are impaired.

Beyond the anticholinergic burden, we identified other iatrogenic sources of cognitive impairment in BD, such as the use of lithium and antipsychotics. Other cross-sectional studies reported a weak and inconsistent negative association between cognition and the use of lithium in euthymic BD (Wingo et al., 2009). However, it was not possible to conclude a causal link between the use of antipsychotics or lithium and cognitive impairment, as we did not investigate the dose effect of these medications on cognition. Longitudinal studies are needed to clarify the effect of antipsychotics and lithium on cognition in BD and should take into account the daily dose and serum levels, duration of exposure, and therapeutic response. Any decision to discontinue antipsychotics or lithium due to cognitive side effects should be made with care after a careful clinical medication review and evaluation of the benefit-to-risk ratio.

In addition, we identified 14 scales with good concurrent validity against peripheral anticholinergic side effects and 13 with good concurrent validity against central anticholinergic side effects in BD. The 15 scales with good validity for at least one of the scores correlated, albeit weakly, with common patient-reported peripheral (such as dry mouth) and central (loss of energy, increased sleep time, and reduced sex drive) anticholinergic side effects. Furthermore, the same scales were all significantly associated with weight gain, which is likely not attributed to anticholinergic properties but to other effects of antipsychotics, mood stabilizers, and antidepressants, which score high on these scales (Vanina et al., 2002). Certain scales were also associated with diarrhea, tremor, vertigo, anxiety, and agitation, which are not generally considered to be anticholinergic side effects. These results suggest that these scales may lack divergent validity, as they were associated with non-anticholinergic side effects. These unexpected associations may arise from the fact that the PRISE-M is a subjective scale that refers to the tolerance of the patients for what they consider to be drug-induced side effects. Patients may have mistakenly considered a symptom of their disorder, such as agitation, as a side effect of the treatment. Besides, the scores of some items, such as loss of energy, can be affected by subclinical mood symptoms. Considering that PRISE-M items are negatively related with self-esteem and psychosocial functioning in resistant depression (Levy et al., 2021), reducing polypharmacy and minimizing the score of the scales associated with peripheral or central subscores could improve the anticholinergic tolerability of psychotropic treatments and patient functioning.

The present study's results may significantly impact clinical decision-making and outcomes in BD. First, when an individual with BD under medication is suspected of experiencing cognitive disorders because of cognitive complaints, altered psychosocial functioning, or after a cognitive screening with a brief tool such as the Screen for Cognitive Impairment in Psychiatry, ATS and Chew's scale are recommended to identify which medication has the most potent anticholinergic properties. Those medications may be switched to treatments with lower scores on the scale when the alternative treatments do not exhibit additional constraints, even before a complete assessment of cognition with a neuropsychological battery. Secondly, when a clinically significant cognitive deficit is identified with an extensive neuropsychological evaluation, Chew's scale may again be used to alleviate the iatrogenic burden on processing speed and reasoning by selecting alternative medication leading to a lower anticholinergic score. In contrast, ATS and Chew are not recommended to manage non-cognitive peripheral and central anticholinergic syndromes. Several other scales had acceptable validity for these syndromes: the strongest associations with peripheral anticholinergic syndrome was found for mARS & Salahudeen's scale, and with central anticholinergic syndrome was found for CALS & Salahudeen's scale. We recommend using these scales to reduce peripheral and central anticholinergic impregnation, especially when it is suspected to impact the quality of life.

The main limitation of our study was the cross-sectional design. Although we controlled for a history of psychosis, the subtype of BD, and the severity of the disorder, our results could be confounded by the indication of the treatment. Cognitively impaired patients may have more anticholinergic treatment than patients with no cognitive impairment because they experience more intense bipolar symptoms or are more regularly hospitalized (Ilzarbe and Vieta, 2023). Secondly, many medications with anticholinergic properties have intense sedative side effects (Balanzá-Martínez et al., 2010), as suggested by the significant associations we measured between the scales and loss of energy or increased sleep time. Yet, sedative side effects are associated with cognitive impairment in BD (Burdick et al., 2015), which might explain the association between the scales and cognitive impairment. Future studies should investigate whether sedation is mediating the associations observed between the scales and cognitive impairment in individuals with BD. Finally, we limited the study to one definition of cognitive impairment, which might have been restrictive. However, using a conservative criterion such as the GDS enabled us to identify the individuals for which the cognitive deficit has the greatest clinical relevance regarding everyday life functioning (Roux et al., 2019).

5. Conclusion

The current management of BD consists largely of pharmacological intervention and our results suggest that anticholinergic burden should be monitored in BD. The variety of available anticholinergic burden scales is considerable, and we recommend using Chew's scale, which presents the best concurrent validity, to identify individuals with remitted BD at risk of iatrogenic cognitive impairment. In addition, Salahudeen's scale exhibits the best concurrent validity against self-reported peripheral & central anticholinergic syndromes and we recommend its use in order to manage non-cognitive anticholinergic side-effects. The use of anticholinergic burden scales appears to be appropriate for

guiding clinicians and researchers in measuring the iatrogenic effects of prescribed treatments.

Contributors

PR, EBG, and NV were responsible for the conceptualization and design of the study. The FACE-BD collaborators were responsible for data collection. PR, NV, EBG, and SF performed the data analysis and drafted the article. All authors contributed to the revision of the manuscript and approved the final version.

Conflicts of interest

All authors declare that they have no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2023.08.502.

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