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Impact of Anticholinergic Burden on Cognitive Functions in Individuals with Bipolar Disorder, Schizoaffective Disorder, and Schizophrenia

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Objective: Bipolar disorder (BD), schizoaffective disorder (SAD), and schizophrenia (SCH) are psychiatric disorders characterized by persistent cognitive impairments, even during periods of remission. Psychotropic medications commonly used to manage these conditions have anticholinergic properties, which may contribute to cognitive impairment.
Methods: This study examined the relationship between anticholinergic medication burden and cognitive function in individuals diagnosed with BD, SAD, and SCH. Anticholinergic burden was assessed using two validated scales, the Anticholinergic Cognitive Burden Scale (ACB) and the CRIDECO Anticholinergic Load Scale (CALS). Cognitive function was evaluated using the Digit Span and the Öktem Verbal Memory Process Test. Retrospective data analysis was conducted to examine the association between anticholinergic medication burden and cognitive performance.
Results: The study included 132 participants including individuals with BD (n = 45), SAD (n = 29), and SCH (n = 58). Higher scores on the ACB and CALS scales were associated with impairments in working memory and immediate memory in the BD group. Similarly, increased anticholinergic burden was associated with immediate memory deficits in the SCH group. However, no significant association was found in the SAD group despite a higher anticholinergic burden.
Conclusion: Our findings highlight the impact of anticholinergic burden on neurocognitive function in individuals with severe psychiatric disorders. The association between anticholinergic burden and cognitive impairment extends beyond SCH spectrum disorders to include BD. These findings underscore the importance of considering anticholinergic burden in psychiatric treatment strategies and call for further research with larger samples to better understand cognitive consequences and refine prescribing practices.

KEY WORDS: Cognition; Cholinergic antagonists; Psychotic disorders; Bipolar disorder.

INTRODUCTION

Individuals diagnosed with schizophrenia (SCH), schizoaffective disorder (SAD), and bipolar disorder (BD), frequently experience cognitive impairments, leading to difficulties in social interactions, occupational activities, and overall well-being [1-4]. Cognitive deficits are among the core features of SCH [5], while other psychotic and affective disorders also manifest milder neuropsychological impairments contributing to functional impairments [6,7].

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The use of psychotropic drugs, especially at high doses, carries a risk of cognitive decline due to their variable anticholinergic properties. Drugs with anticholinergic properties, which are commonly prescribed for psychiatric disorders, act primarily through muscarinic receptors, particularly the M1, M2 and M4 subtypes. These receptors play an important role in cognitive processes such as executive function and memory processing in the central nervous system [8]. The antagonism of these receptors can lead to cognitive disturbances and neuronal cell death [9]. Both first-generation antipsychotics (AP) and second-generation AP, particularly in high doses or in polypharmacy, can cause cognitive decline [10-13]. Patients are also prescribed anticholinergic drugs to treat extrapyramidal side effects of antipsychotic drugs [14]. In addi-

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tion to drugs known to have significant anticholinergic effects like AP and certain antidepressants (AD), lithium, and valproate also have slight anticholinergic effects [15]. The anticholinergic effect of valproate is known to be better than that of carbamazepine and oxcarbazepine [16].

The use of polypharmacy, which is sometimes necessary for treating severe psychiatric illnesses such as psychotic or BDs, increases the possibility of anticholinergic burden, and therefore careful use of polypharmacy is emphasized. A recent review focusing on the anticholinergic burden in SCH reported associations between anticholinergic burden and declines in various memory types (declarative, verbal, short-term), as well as in the domains of learning and language/verbal skills. In light of these findings, clinicians are advised to reassess the need for anticholinergic treatment and to exercise caution in prescribing medications with known anticholinergic activity before considering cognitive rehabilitation interventions in individuals with severe mental illness [17].

The association between anticholinergic burden and cognitive impairment has been studied primarily in the psychotic spectrum [18-20]. To our knowledge, only two studies have investigated this relationship in BD, with conflicting findings [21,22]. The anticholinergic scales used in the studies also vary. There are several anticholinergic measuring tools to assess the total anticholinergic burden of drugs [13,23-27]. Our study aims to assess the impact of anticholinergic burden on various memory processes and to explore potential associations between anticholinergic burden scores and neurocognitive impairment particularly in individuals with BD, focusing on digit span and verbal memory tests. We also planned to assess this association in individuals with SAD, and SCH. We chosed to use the most recent version, the CRIDECO Anticholinergic Load Scale (CALS), as it covers a wider range of psychotropic medications and includes anticholinergic medications in the list [23] and the Anticholinergic Cognitive Burden Scale (ACB) which is the most commonly used anticholinergic burden scale [27]. Finally, we seek to provide insights into the potential implications for prescribing practices in these psychiatric populations.

METHODS

The study included individuals who were referred to Pamukkale University Psychiatric Hospital between 2020 and 2023 for assessment of their level of functioning. Inclusion criteria included individuals between the ages of 18 and 65 who were diagnosed with BD, SAD, or SCH according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria and those who underwent neurocognitive testing. Exclusion criteria included missing sociodemographic data, psychotropic medication details, duration of illness (year), and hospitalization history. Individuals with recent ECT treatment within the last six months, recent inpatient treatment within the last three months, and comorbid conditions such as intellectual disability, attention deficit and hyperactivity disorder, dementia, and substance use disorders were excluded. A total of 48 patients were excluded according to the exclusion criteria. As part of the functional level assessment, a face-to-face interview was conducted with all patients in the outpatient clinics. Experienced clinicians (MD psychiatrists) carried out the diagnostic interviews and experienced psychologists carried out the neurocognitive tests. Sociodemographic data, psychotropic medication and illness characteristics (duration of illness, number of hospitalisations), and neuropsychiatric test scores were collected from hospital records. Disorder states were classified as chronic/continuous, remission and partial remission according to the DSM-5 [28].

The Öktem Verbal Memory Process Test (VMPT) is used for the assessment of verbal memory [29]. The verbal memory processes evaluation includes the examination of immediate memory score, total acquisition score (the total number of words recalled), the highest learning point (the maximum number of words remembered in trials), and long-term recall, total recall (long-term recall plus recognition) scores are assessed. The Digit Span test has two subtests; the Digit Span Forward task evaluates immediate memory, specifically short-term auditory memory, by asking participants to repeat a sequence of numbers in the same order as presented. The Digit Span Backward task assesses working memory by requiring participants to repeat a sequence of digits in the reverse order in which they were presented [30].

CALS and ACB were used to measure anticholinergic burdens. In both ACB and CALS, drugs are ranked from 1 (lowest) to 3 (highest) according to their anticholinergic potency. Unlike the most commonly used cholinergic scale ACB, CALS places olanzapine, quetiapine, and pa-

roxetine in level 2. Fluphenazine and zuclopenthixol each score 2. Biperiden is given 3 points and amisulpride and lithium are given 1 point each. We updated the ACB scale following the methods described by Joshi *et al.* [18] and added 3 points for biperiden, which is commonly used as an anticholinergic in our sample. Chlorpromazine equivalents for antipsychotic doses were determined according to Leucht *et al.* [31].

Statistical analyses were performed using the SPSS 25.0 package program (IBM Co.) for MacOS. The normality of distribution for these variables was determined by examining skewness and kurtosis. Variables with skewness and kurtosis values between −2 and +2 were considered normally distributed, following the guideline established by George and Mallery [32]. There is no one-size-fits-all rule for sample size calculation in linear regression. In the current study BD and SCH groups consisted of 45 and 58 patients respectively. While these numbers may be considered adequate according to some views [33,34], they should be 66 (for 2 predictors) and 74 (for 3 predictors), respectively, when calculated according to the frequently used Green's rule of thumb [35]. Group comparisons in categorical variables were analyzed with the chi-squared test. One-way ANOVA test was used to compare the quantitative variables and Bonferroni correction was used for post-hoc comparisons. Correlations between neurocognitive test scores and anticholinergic burden scale scores were assessed using Pearson correlation analysis for the SCH and the BD groups. However, due to the small sample size in the SAD group, non-parametric Spearman correlation analysis was conducted for the SAD group. Multiple linear regression analyses (stepwise method) were used to investigate the association between neurocognitive tests and anticholinergic burden scales. In these analyses, variables (e.g. age, duration of education [years], duration of illness [years], and equivalent chlorpromazine dosages) that were determined to show a significant correlation with each neurocognitive test score were included as independent variables. Since correlation analyses in the SAD group already showed that there was no significant relationship between the variables, linear regression analyses were not performed in this group. Ethical approval was obtained on January 15, 2024, from the Pamukkale University Ethics Committee. Ethical approval was obtained on January 15, 2024, from the Pamukkale University Ethics Committee (approval number: 476166).

RESULTS

Study Sample

A total of 132 patients were included in the study. The number of individuals in the patient groups was as follows: 45 for BD (25 females, 20 males), 29 for SAD (12 females, 17 males), and 58 for SCH (15 females, 43 males). The mean age of all participants was 40.29 ± 9.91 years. The mean number of hospitalizations for the entire sample was 2.13 ± 2.07, the mean duration of education (years) was 9.91 ± 3.89, and mean duration of illness (years) was 14.23 ± 8.09. According to the DSM-5, 22% of patients were classified as chronic/continuous, 50.8% were in partial remission and 27.3% were in remission.

There was no significant difference in the mean age, duration of education (years), and duration of illness (years) between the three groups. Notably, the number of hospitalizations was significantly higher in the SAD group compared to the SCH group ($p < 0.001$) (Table 1).

When examining the medication usage percentages of the patients; it is observed that 0.8% of the patients use mood stabilizers only (MS), 31.8% use AP only, 0.8% use both AD and MS, 43.2% use both AP and MS, 8.3% use a combination of AP, AD, and MS, and 15.2% use both AP and AD. While 30.3% of the patients take 1 or fewer APs, 60.7% use 2 or more combinations of APs. The mean chlorpromazine equivalent doses of the patient groups were 748.80 ± 457.94, and there were significant differences between the groups (BD-SAD < 0.001, BD-SCH < 0.001, SAD-SCH: 0.077). A total of 17 (12.8%) patients in the sample were taking biperiden as an anticholinergic medication.

The sociodemographic features and clinical characteristics of the groups are shown in Table 1.

Neurocognitive Tests and Anticholinergic Burdens

The neurocognitive test scores in the whole group were as follows: digit span forward 4.62 ± 1.89, digit span backward 3.74 ± 1.56, immediate memory 4.07 ± 1.62, total acquisition score 72.14 ± 23.14, highest learning point 9.79 ± 2.91, long term recall 7.70 ± 3.57, total recall 13.07 ± 2.88. Comparisons of neurocognitive test scores and anticholinergic burden scores among groups are presented in Table 2.

Table 1. Sociodemographic and clinical features of the sample

		BD (n = 45)	SAD (n = 29)	SCH (n = 58)	Chi-square / F	*p*
Sex	Male	20 (44.4)	17 (58.6)	43 (74.1)	9.419	0.009*
	Female	25 (55.6)	12 (41.4)	15 (25.9)		
Remission with treatment	Chronic/continuous	2 (4.4)	8 (27.6)	19 (32.8)	19.329	0.001*
	Partial remission	23 (51.1)	18 (62.1)	26 (44.8)		
	Full remission	20 (44.4)	3 (10.3)	13 (22.4)		
Age (yr)		39.95 ± 11.25	40.58 ± 9.34	40.41 ± 9.21	0.042	0.958
Duration of education (yr)		10.82 ± 3.67	9.75 ± 3.87	9.27 ± 4.00	2.054	0.132
Duration of illness (yr)		12.84 ± 8.77	14.55 ± 5.07	15.13 ± 8.71	1.049	0.353
Hospitalization (n)		2.15 ± 2.12	3.20 ± 2.24	1.58 ± 1.74	6.391	0.002*
Chlorpromazine equivalent doses (mg/day)		498.51 ± 363.69	962.59 ± 444.36	836.08 ± 44.89	12.926	< 0.001*

Values are presented as number (%) or mean ± standard deviation.
*$p < 0.05$.
BD, bipolar disorder; SAD, schizoaffective disorder; SCH, schizophrenia; n, number.

Table 2. Comparisons of neurocognitive test scores and anticholinergic burden scores of BD, SAD, and SCH groups

	BD (n = 45)	SAD (n = 29)	SCH (n = 58)	F	*p*
Digit Span Test					
Forward	5.02 ± 2.01	4.13 ± 1.74	4.56 ± 1.84	1.983	0.142
Backward	3.97 ± 1.63	3.65 ± 1.58	3.61 ± 1.50	0.727	0.485
Verbal Memory Processing Test					
Immediate memory	4.37 ± 1.55	3.89 ± 1.97	3.93 ± 1.48	1.182	0.310
Total acquisition	78.93 ± 23.74	71.46 ± 25.58	67.32 ± 20.42	3.272	0.041*
Highest learning point	10.68 ± 3.12	10.04 ± 2.99	9.03 ± 2.54	4.090	0.019*
Long-term recall	8.75 ± 3.56	7.34 ± 3.75	7.06 ± 3.36	3.102	0.048*
Total recall	13.64 ± 2.60	12.82 ± 3.04	12.75 ± 2.99	1.388	0.266
Anticholinergic Burden Scales					
CALS score	3.55 ± 1.54	5.10 ± 2.28	4.17 ± 1.83	6.138	0.003*
ACB score	3.86 ± 1.58	5.68 ± 2.20	4.56 ± 2.10	7.281	0.001*

Values are presented as mean ± standard deviation.
*$p < 0.05$.
BD, bipolar disorder; SAD, schizoaffective disorder; SCH, schizophrenia; ACB, Anticholinergic Cognitive Burden Scale; CALS, CRIDECO Anticholinergic Load Scale; n, number.

There were significant differences between BD and SCH in total acquisition scores and highest learning points (total acquisition, $p = 0.036$; highest learning point, $p = 0.017$; long-term recall, $p = 0.052$).

The mean CALS score for the whole sample was 4.16 ± 1.92. The SAD group had a significantly higher mean CALS score than the BD group ($p = 0.002$). The mean ACB score for the total sample was 4.56 ± 2.10. The mean ACB score of the SAD group was significantly higher than that of the BD ($p < 0.001$) and SCH ($p = 0.038$) groups.

Anticholinergic Burden Impact on Neurocognitive Tests

Duration of education (years) ($r = 0.331$, $p = 0.028$) and ACB ($r = -0.415$, $p = 0.005$) were significantly correlated with digit span forward in the BD group. Digit span backward was significantly correlated with duration of education (year) ($r = 0.427$, $p = 0.004$), chlorpromazine equivalent dosage of antipsychotic medications ($r = -0.489$, $p = 0.001$), ACB scores ($r = -0.522$, $p < 0.001$) and CALS scores ($r = -0.519$, $p < 0.001$). No correlations were found between anticholinergic burden scores and neurocognitive test scores in the SAD group (according to Spearman correlation analysis, in all analyses $p > 0.05$). For the SCH group, variables significantly correlated with immediate memory included age ($r = -0.307$, $p = 0.019$), duration of education (year) ($r = 0.434$, $p = 0.001$), CALS ($r = -0.266$, $p = 0.044$), and ACB scores ($r = -0.334$, $p = 0.010$). However, there were no significant correlations

Table 3. Regression analyses of neurocognitive test scores and anticholinergic burden in BD groups

Dependent variable	Independent variables	Predictors	Unstandardized coefficients		Standardized coefficients	*t*	Significance	Adjusted R^2
			B	SE	Beta			
Digit span forward	Duration of education (yr), ACB	ACB	−0.529	0.179	−0.415	−2.953	0.005	0.152
Digit span backward	Duration of education (yr), CALS	CALS	−0.513	0.127	−0.485	−4.044	< 0.001	0.387
		Duration of education (yr)	0.170	0.053	0.383	3.199	0.003	
Digit span backward	Duration of education (yr), ACB	ACB	−0.465	0.131	−0.450	−3.553	0.001	0.463
		Duration of education (yr)	0.145	0.056	0.328	2.589	0.013	
		Chlopromazine equivalent dosage	−0.001	0.001	−0.326	−2.558	0.014	
Immediate memory	Age, CALS	CALS	−0.356	0.144	−0.354	−2.480	0.017	0.105

ACB, Anticholinergic Cognitive Burden Scale; CALS, CRIDECO Anticholinergic Load Scale; SE, standard error; BD, bipolar disorder.

Table 4. Regression analyses of neurocognitive test scores and anticholinergic burden in SCH groups

Dependent variable	Independent variables	Predictors	Unstandardized coefficients		Standardized coefficients	*t*	Significance	Adjusted R^2
			B	SE	Beta			
Immediate memory	Age, duration of education (yr), CALS	Duration of education (yr)	0.155	0.044	0.419	3.568	0.001	0.218
		CALS	−0.193	0.095	−0.239	−2.036	0.047	
Immediate memory	Age, duration of education (yr), ACB	Duration of education (yr)	0.154	0.042	0.416	3.637	0.001	0.258
		ACB	−0.210	0.078	−0.310	−2.709	0.009	

CALS, CRIDECO Anticholinergic Load Scale; ACB, Anticholinergic Cognitive Burden Scale; SE, standard error; SCH, schizophrenia.

between anticholinergic burden scales and other neurocognitive test scores.

The multivariate linear regression analyses, using the variables identified in the earlier correlation analysis as independent variables, and the neurocognitive test scores as dependent variables are presented in Tables 3, 4. If either the ACB or CALS scores showed a statistically significant correlation with neurocognitive test scores, that scale was included in the linear regression analysis. In cases where both scales showed significant correlations with the same neurocognitive test scores, separate linear regression analyses were conducted for the ACB and CALS scores. In the BD group, both ACB and CALS scores were associated with decreased digit span backward scores. Furthermore, in the BD group, ACB scores were associated with a decrease in digit span forward, while CALS scores were associated with a decrease in immediate memory. Similarly, in the SCH group, ACB and CALS scores were associated with a decrease in immediate memory scores. However, no significant association was observed between these anticholinergic burden scales and test scores in the SAD group.

DISCUSSION

The relationship between anticholinergic burden, evaluated through ACB and CALS scores, and neurocognitive test performance (Digit Span, VMPT) in the BD, SAD, and SCH groups was evaluated in this study. Impairments in immediate memory were associated with both ACB and CALS scores in both the BD and SCH groups. Impairments in working memory were also associated with both ACB and CALS scores particularly in the BD group. However, no significant relationship was observed between anticholinergic load and cognitive function in the SAD group.

In this study, a negative association was found between anticholinergic burden and working and immediate memory in individuals with BD. This association was observed using both the ACB, which is commonly used in studies of anticholinergic exposure, and the CALS, a more

recent measure. Prior to our study, only two studies had investigated the association between anticholinergic burden and cognitive functions in BD [21,22]. Eum *et al.* [21] found no significant association between Anticholinergic Drug Scale (ADS) and cognitive scores using the Brief Assessment of Cognition in Schizophrenia (BACS) study. The BACS includes Verbal Memory, Digit Sequencing, Token Motor, Verbal Fluency, Symbol Coding, and Tower of London tests. On the other hand, Vidal *et al.* [22] demonstrated a weak association between Chew's scale and impaired processing speed and judgment in individuals with BD from the FACE-BD cohort. In that study, Digit Symbol Coding, WAIS Symbol Search, Trail Making Test Part A for processing speed, WAIS Digit Span and Spatial Span, Conners' Continuous Performance Test, Stroop test, verbal fluency tests, and Trail Making Test Part B, along with WAIS vocabulary and matrices were used.

This study and two others, used different anticholinergic burden scales. The ADS uses existing research and expert opinions to categorize drugs based on their anticholinergic potency. Conversely, the Chew Scale focuses solely on a drug's direct anticholinergic activity measured in laboratory settings. Meanwhile, ACB and CALS rely on a combination of systematic reviews of drugs with known anticholinergic properties and expert input to assign burden scores. This diversity in scale design highlights the different approaches utilized to quantify the anticholinergic potential of medications. On the other hand, Vidal *et al.* [22] stated that if the drug was not included in a scale, they would give that drug a score of zero on that scale. We specifically gave biperiden 3 points even though it is not included in the scale. This may be related to the fact that they could not show a relationship between scales other than the Chew Scale and cognitive function.

The Verbal Memory Test (VMPT) used in our study may have some similarities to the Verbal Memory Test used by Eum *et al.* [21]. However, our study differed in two key methodological aspects. Firstly, we used the backward version of the Digit Span Test to assess working memory, which was not included in Eum *et al.* [21]'s study using the BACS. Secondly, we used the ACB and CALS scales to evaluate anticholinergic burden, whereas their study did not address this factor. These methodological discrepancies may explain the different findings between our investigation and Eum *et al.* [21]'s research. Furthermore, the neuropsychological test battery used in our study differs from that used by Vidal *et al.* [22]. While our verbal memory assessment (VMPT) might be comparable, Vidal *et al.* [22] included a more comprehensive battery encompassing tests for processing speed, working memory (both forward and backward digit span), attention, executive function, and verbal and perceptual reasoning. Although the tests used in our study were not primarily designed to assess executive function, we did include a detailed assessment of immediate memory and recall. Differences in the cognitive tests used in the studies may have led to different results.

Moreover, mean chlorpromazine equivalent doses were lower in the BD group, although anticholinergic burden scores were not significantly different from those in the SCH group. At this point, it should be noted that more frequent use of drug combinations (whether antipsychotic drug combinations or other drug combinations) for symptomatic relief may increase anticholinergic load, increase cognitive problems, and ultimately have a negative impact on functionality. In this case, combinations included mainly MS, anticonvulsants, AD and AP in BD.

Anticholinergic drugs, which are commonly used for psychiatric conditions, primarily target the brain's cholinergic system, which is important for attention and memory. This means that these drugs are likely to impair attention and memory processes due to their effects on the cholinergic system [36]. Our study is in line with the existing literature, which indicates a decline in different types of memory (short-term and working) with increasing anticholinergic exposure, as highlighted in the review by Georgiou *et al.* [17]. Joshi *et al.* [18] also reported no significant effect of AP on cognitive test scores after controlling for the effect of ACB score. In a recent 21-year follow-up cohort evaluating the long-term effects of anticholinergic exposure in patients with first-episode psychosis, they found that cumulative anticholinergic exposure negatively affected cognition [37]. They suggested that several years of anticholinergic exposure may be required for cognitive changes to occur. The mean ACB scores of our samples were quite high (4.56 ± 2.10). In addition, our results show a relatively higher anticholinergic burden within the SAD group, possibly due to the frequent use of multiple AP and other treatment modalities to manage their symptoms. However, we did not observe an association between anticholinergic exposure and cognitive function.

In this study it was found that the digit span performance of BD, SAB and SCH patients was similar. However, individuals with BD showed higher levels of total acquisition and maximum learning performance compared to individuals with SCH. Previous studies have observed cognitive deficits in SCH in various cognitive domains, including verbal learning and memory, verbal fluency, working memory, processing speed, and executive function [6]. Individuals with BD also show cognitive impairments in various cognitive domains, even during the euthymic phase [38-40]. While some studies suggest differences in specific cognitive domains between BD and SAD, others find no significant differences [41,42]. In addition, studies investigating SAD have also found significant impairments in verbal learning and memory [43,44]. Hill *et al.* [6] suggest that SAD exists on a spectrum between BD and SCH, with affective symptoms being more prevalent and associated with less cognitive impairment. As this study did not specifically address the effects of lithium and other MS, we did not perform further analyses to differentiate drug effects due to the small sample size and different combinations of psychotropic medications in the BD and SAD groups.

Although data on the severity of patients' disorders were not available in our study, we did have data on the remission status of patients with BD, SAD and SCH. The remission status of our sample was similar to that reported in a recent prospective cohort study [37]. In particular, the SAD group appeared to have a lower rate of complete remission, suggesting a more challenging disease course in this group. It is important to emphasize that this study was not designed in a prospective, randomized or controlled manner and is a retrospective study. In addition, the anticholinergic burden was only calculated for psychotropic drugs. However, in a nationwide study, a high anticholinergic burden was found to be mainly due to psychotropic drugs [45]. A high anticholinergic burden was observed in all groups, including the BD subgroup. In addition, the lack of measures to define disease severity introduces ambiguity, as patients with more severe psychopathology may have been treated with drug combinations resulting in a higher anticholinergic load. In an alternative classification based on cognitive performance in BD, some authors have identified three cognitive subtypes: no cognitive impairment, partial cognitive impairment, and impairment in all cognitive domains [46]. These subtypes are a separate classification from the clinical subtypes. Cognitive subtypes have been found to be strongly related to social functioning [47]. It has been suggested that the cognitive classification approach may help to determine the risk of disease progression [48]. This makes the prescribed medication even more important.

This study found a clear association between anticholinergic load and cognitive function in the BD group. However, this association was not found in the SAD group, despite a relatively high anticholinergic burden. Several factors could explain this discrepancy. First, pre-existing cognitive impairment in the SAD group could mask the effects of anticholinergic medications on performance. Secondly, the severity of SAD itself could play a role. Compared to the BD group, SAD patients had more hospitalisations, suggesting potentially greater disorder severity and functional impairment. This could also contribute to the lack of correlation observed. Additionally, a higher proportion of patients with pre-existing severe cognitive deficits within the SAD group could be another explanation. In contrast, the BD group, characterized by a lower anticholinergic load, exhibited a correlation between cognitive function and anticholinergic burden. This aligns with previous research suggesting a stronger association when baseline cognitive performance is closer to normal [20].

This study has several limitations. The retrospective design makes it difficult to establish a definitive cause and effect relationship between anticholinergic medication use and cognitive outcomes. In addition, the small sample sizes in all groups is an important limitation. We were not able to distinguish between BD subtypes (e.g. bipolar I disorder, bipolar II disorder) in our analysis. Evaluating the effects of anticholinergic medications on cognitive function within different bipolar subtypes, including those with and without psychotic features, may provide valuable insights. Factors such as symptom profiles, specific medications used, and the level of functional impairment and severity of the illness may all contribute to these contrasting findings. Factors such as levels of anxiety and depression which can affect cognitive function, and the sedative side effects of the medications used may also have influenced the results. The inability to assess the effect of these factors is another limitation. The lack of data on other drugs with anticholinergic properties (e.g., for asthma or urinary problems) is a major limitation.

Future research with larger sample sizes and more homogenous participant groups is needed to gain deeper insights into the complex interplay between anticholinergic medications and cognitive function in individuals with BD, SAD, and SCH. It is also important to investigate the effects of anticholinergics in patients with lower medication exposure, particularly in larger and more representative SAD samples. Longitudinal studies that follow cognitive changes over time would further improve our understanding of these relationships.

Although cognitive function has been extensively studied in BD, SAD and SCH, there is a paucity of research specifically investigating the relationship between anticholinergic load and cognitive function. Our study sheds light on the decline in working and immediate memory that correlates with anticholinergic exposure in the BD and SCH groups, highlighting the importance of this association, particularly in BD. Further research is needed to assess the lasting cognitive effects of anticholinergic load in more homogeneous groups and how reducing anticholinergic load may provide valuable insights to optimize prescribing practices and improve long-term patient outcomes.

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■ **Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

■ **Author Contributions**

Conceptualization: Nilgun Oktar Erdogan. Data acquisition: Nilgun Oktar Erdogan. Formal analysis: Nilgun Oktar Erdogan, Bengu Yucens, Selim Tumkaya. Writing—original draft: Nilgun Oktar Erdogan. Writing—review & editing: Bengu Yucens, Selim Tumkaya.

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