Anticholinergic Burden and Cognitive Function in Psychosis: A Systematic Review and Meta-Analysis

Valentina Mancini, M.D., Ph.D., Caren Latreche, M.Sc., Jack B. Fanshawe, M.B.Ch.B., Ioana Varvari, M.R.C.Psych., Chambrez-Zita Zauchenberger, M.B.Ch.B., M.Sc., Nova McGinn, B.Sc., Ana Catalan, M.D., Ph.D., Toby Pillinger, M.R.C.Psych., Ph.D., Philip K. McGuire, M.R.C.Psych., Ph.D., Robert A. McCutcheon, M.R.C.Psych., Ph.D.

Objective: The authors synthesized evidence from studies quantifying the relationship between anticholinergic medication and cognitive function in psychosis, and additionally explored studies that investigated whether reducing anticholinergic medications affects cognitive function in individuals with psychosis.

Methods: A database search was conducted in MEDLINE, Embase, and PsycINFO, from database inception to October 2023, for studies reporting objective cognitive assessment and quantification of anticholinergic burden using clinical scales, serological anticholinergic activity, or tapering of anticholinergic medications. Analyses were carried out in R using the *metafor* package. Random-effects meta-analysis models were employed, along with assessment of heterogeneity, study quality, and meta-regressions (age, sex, and antipsychotic dosage in chlorpromazine equivalents).

Results: Of 1,337 citations retrieved, 40 met inclusion criteria, comprising 25 anticholinergic burden studies (4,620 patients), six serological anticholinergic activity studies (382 patients), and nine tapering studies (186 patients). A negative correlation was identified between anticholinergic burden and global cognition (r=−0.37, 95% CI=−0.48, −0.25), verbal learning (r=−0.28, 95% CI=−0.36, −0.21), visual learning (r=−0.17, 95% CI=−0.28, −0.06), working memory (r=−0.22, 95% CI=−0.29, −0.14), processing speed (r=−0.24, 95% CI=−0.35, −0.13), attention (r=−0.19, 95% CI=−0.29, −0.08), executive functions (r=−0.17, 95% CI=−0.27, −0.06), and social cognition (r=−0.12, 95% CI=−0.19, −0.05), and between serological anticholinergic activity and verbal learning (r=−0.26, 95% CI=−0.38, −0.14), working memory (r=−0.19, 95% CI=−0.35, −0.03), and executive functions (r=−0.16, 95% CI=−0.27, −0.04). Finally, tapering off anticholinergic medication improved the scores in verbal learning (d=0.77, 95% CI=0.44, 1.1), working memory (d=0.94, 95% CI=0.63, 1.26), and executive functions (d=0.44, 95% CI=0.26, 0.62).

Conclusions: Anticholinergic burden is associated with the cognitive impairments observed in psychosis. From a clinical perspective, tapering off anticholinergic medication in patients with psychosis may improve cognition. However, randomized clinical trials are needed for an unbiased quantification of benefit.

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Cognitive deficits are increasingly recognized as a core feature of psychosis, with approximately 80% of affected individuals exhibiting clinically relevant impairment (1). On average, the cognitive performance of people with psychosis is two standard deviations below that of the general population (2). This contributes to poor functional outcomes and overall disability (3), leading to high rates of unemployment and the need for long-term community support (4), which result in increased health care costs (5). Antipsychotics alleviate the burden of positive psychotic symptoms by targeting the dopaminergic system, but do not significantly improve cognitive symptoms (6). Indeed, antipsychotics have deleterious cognitive effects, exacerbating preexisting deficits (7).

Cholinergic neurotransmission plays a crucial role in regulating the circuit dynamics that underlie cognitive processing (8). Cholinergic projection neurons arising from mid- and forebrain nuclei project extensively to the cerebral cortex, hippocampus, and amygdala (9). Acetylcholine exerts its effect through two different types of receptors: ionotropic nicotinic receptors and muscarinic G protein–coupled metabotropic receptors. M1 receptors are the most abundant muscarinic subtype in the cerebral cortex and hippocampus (10), and M1 knockdown mice exhibit profound deficits in working memory and consolidation (11).

In both healthy control subjects and individuals with psychosis, the administration of cholinergic antagonists is associated with cognitive impairments (12). Furthermore, cholinergic antagonism appears to have the potential to induce a range of psychotic symptoms (13). Conversely, augmentation of cholinergic signaling is a well-established

treatment strategy for the cognitive impairments of Alzheimer's disease (14), and more recently muscarinic agonism has been demonstrated to have an antipsychotic, and potentially procognitive, effect in schizophrenia (15–18).

Despite their deleterious cognitive properties, compounds that competitively inhibit the binding of acetylcholine to muscarinic receptors are routinely prescribed for people with psychosis, for example, as treatments for extrapyramidal side effects of antipsychotics (19). Furthermore, several psychotropic medications across different pharmacological classes exhibit various degrees of anticholinergic effect, despite this effect not being implicated in their principal therapeutic mechanism. Among antipsychotics, olanzapine, clozapine, and quetiapine display significant cholinergic receptor affinity, leading to cholinergic side effects (20). Additionally, anticholinergic properties are found in several antidepressants, antiepileptics, and antihistamines. Multimorbidity and polypharmacy are common among people with chronic psychosis (21, 22), further increasing the likelihood of a high anticholinergic burden. Over the years, clinical scales have been developed to quantify anticholinergic properties of commonly used medications, allowing the estimation of the cumulative pharmacological anticholinergic burden in each patient (23–26).

Several studies have investigated the association between anticholinergic burden and cognitive impairment in schizophrenia. Some of these studies have estimated anticholinergic burden through clinical scales, some have directly measured the serum anticholinergic activity in each patient, and some have assessed the impact of reducing anticholinergic burden. These, however, have not yet been meta-analytically synthesized. Our aim in the present study was to undertake a meta-analysis to provide a complete and quantitative description of the relationship between anticholinergic exposure and cognitive function in psychosis.

METHODS

This meta-analysis was registered with PROSPERO (CRD42023447185) and followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines (see the online supplement).

Search Strategy

We searched MEDLINE, Embase, and PsycINFO from database inception through October 3, 2023, using the following keywords: ("schiz*" OR "psychosis" OR "prodrom*" OR "at risk mental state" OR "high risk mental state" OR "ultra high risk" OR "clinical high risk") AND ("anticholinergic" OR "cholinergic") AND ("cognition" OR "cognitive" OR "memory" OR "attention" OR "processing speed" OR "executive function" OR "learning").

Inclusion and Exclusion Criteria

We included observational studies or clinical trials in individuals over 18 years of age with diagnoses across the psychosis spectrum, including schizophrenia, first-episode psychosis, and psychotic mood disorders, as well as individuals at clinical high or ultra-high risk for psychosis (see Table S1 in the online supplement) in three categories:

1. Studies assessing cognitive functioning using standardized tools (for a comprehensive list of the cognitive scales, tests, and subtests used in the studies included in this meta-analysis, see Table S2 in the online supplement).
2. Studies reporting clinical or serological measures of anticholinergic medication burden, such as the Anticholinergic Cognitive Burden scale, the Anticholinergic Burden Calculator, the Anticholinergic Burden Scale, the Anticholinergic Drug Scale, the Drug Burden Index, and serum anticholinergic activity, or, alternatively reporting the results of a challenge or tapering of medications with cholinergic activity.
3. Studies providing data enabling either the estimation of the correlation between the extent of anticholinergic burden and relevant cognitive parameters or a standardized mean difference in cognition between individuals with high versus low anticholinergic burden (or before and after anticholinergic medication tapering, or anticholinergic medication challenge).

We excluded studies of patients with a primary axis I diagnosis other than psychosis (such as nonpsychotic mood disorders, anxiety disorders, and pervasive developmental disorders; studies that included patients with psychosis with a psychiatric comorbidity were still eligible) and studies reporting nonquantitative measures of cognitive assessment, such as clinical qualitative interviews and self-report scales. If papers only reported adjusted coefficients, we contacted the authors to request data that were not corrected for the effect of covariates. If the authors did not reply, the study was excluded.

DATA EXTRACTION AND PROCESSING

Abstracts of articles identified were screened by pairs of independent investigators (V.M., C.L., J.B.F., I.V., C-Z.Z., and N.M.), and after those that were not relevant were excluded, the full texts were assessed for eligibility. Discrepancies were adjudicated by any other rater not involved in the screening of the papers in the previous rounds, and the final decision was made by V.M. and R.A.M. We extracted Pearson correlation coefficients for studies examining the correlation between anticholinergic burden and cognitive measures. For studies comparing patients with high versus low anticholinergic burden, or between patients before and after anticholinergic medication tapering or challenge, we extracted the mean cognitive measure with the associated standard deviation, standard error, or confidence interval.

As previously reported (27, 28), we grouped the cognitive tests from the selected papers into domains from the Measurement and Treatment Research to Improve Cognition in

Schizophrenia (MATRICS) battery (29). The seven cognitive domains included in the MATRICS are speed of processing, attention, working memory, verbal learning, visual learning, reasoning and problem solving (referred to hereafter as executive functions), and social cognition. Additionally, composite scores (referred to hereafter as global cognition scores) were extracted.

Statistical Analysis

All analyses were carried out in R, version 4.3.2, using the *metafor* package. Because we expected high heterogeneity due to the differences in study methodology, we employed a random-effects meta-analysis model. We used the Cochrane Q statistic and I^2 index to assess heterogeneity (30). Effect sizes were estimated as r values for correlational studies (anticholinergic burden and serological anticholinergic activity) and as standardized mean difference (Cohen's d) for tapering studies. Bonferroni correction for multiple comparisons was applied to all the individual meta-analyses, correcting for the number of cognitive domains (for instance, for the main analyses, N=8 for the anticholinergic burden studies, N=3 for the serological anticholinergic activity studies, and N=4 for the tapering studies). All p values presented are Bonferroni corrected.

When studies of anticholinergic burden reported only dichotomous measurements, we followed standard statistical approaches to estimate the corresponding biserial correlation coefficient, as previously described (31). First, we calculated the standardized mean difference between the two groups, which we then converted into the point-biserial correlation coefficient. Finally, the point-biserial correlation was transformed into the biserial correlation coefficient (31).

Publication bias was evaluated by visually inspecting funnel plots and performing Egger's test where there were at least 10 studies (32). In case of funnel plot asymmetry or statistically significant Egger's test, we performed a trim-and-fill analysis (33). Study quality was evaluated using the Newcastle-Ottawa Scale for observational studies (34). Meta-regression analyses were conducted to evaluate the effect of age, sex, chlorpromazine-equivalent antipsychotic dosage, and scores from the Newcastle-Ottawa Scale on the outcomes of interest where there were at least 10 studies (35).

We conducted two sensitivity analyses, the first excluding studies in which the anticholinergic burden was quantified as the dosage of anticholinergic medications rather than the cumulative anticholinergic burden arising from all the medications taken by each patient, and the second excluding studies in which cognitive outcomes were measured before and after a challenge with an anticholinergic medication rather than tapering off anticholinergic medications.

Finally, we conducted two additional sensitivity analyses, the first including only studies in which anticholinergic burden was estimated using the Anticholinergic Cognitive Burden scale, and the second including only studies in which the participants were first-episode psychosis patients (rather than patients with a full-blown psychotic disorder).

The difference between individuals with first-episode psychosis and those with a diagnosis of schizophrenia was evaluated by using a Wald-type test to test the difference between the estimated average log risk ratios from each meta-analysis (36).

RESULTS

Study Characteristics

A total of 1,337 articles were identified by the search; 213 subsequently underwent full-text screening, and 40 were included in the meta-analysis (see Figure 1 for the PRISMA flowchart and Table S1 in the online supplement for a description of all the studies included). Overall, 5,188 individuals with psychosis were included in the synthesis (mean age, 38.6 years [SD=12.8, range=18–68]; 3,333 [64.5%] were male), of whom 87.6% (N=4,543) had a diagnosis of schizophrenia and 12.4% (N=645) a diagnosis of first-episode psychosis. All the participants included were treated with antipsychotic medication, and the mean chlorpromazine-equivalent dosage was 506.5 mg/day (SD=53.6, range=270–1,042).

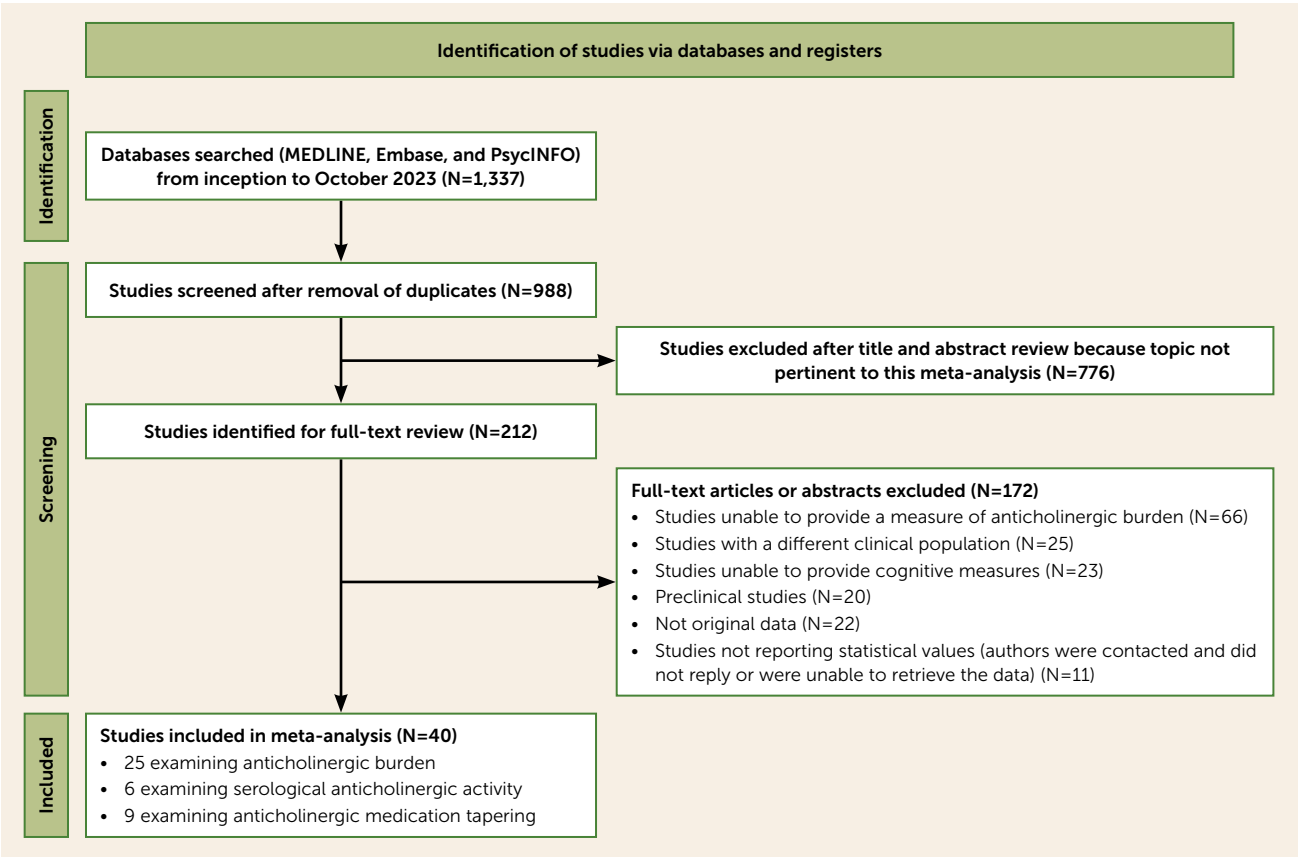
The studies were divided into three categories, depending on the measure of anticholinergic burden (see Figure 1; see also Table S1 in the online supplement):

- Twenty-five studies examining anticholinergic burden through clinical scales (37–52) or anticholinergic medication dosage (53–61) (total N=4,620; mean age, 38.4 years [SD=12.7, range=18–65]; 2,980 [64.5%] were male).
- Six studies examining serological anticholinergic activity (62–67) (total N=382; mean age, 35.8 years [SD=11.8, range=18–65]; 267 [69.9%] were male).
- Nine studies comparing cognitive function in individuals before and after tapering or challenge with anticholinergic medications (68–76) (total N=186; mean age, 54.9 years [SD=14.2, range=18–68]; 88 [47.3%] were male); study arms before tapering or after the challenge with anticholinergic medications were categorized as exposed to anticholinergic medication, while the arms after tapering or before the challenge were categorized as anticholinergic free.

Correlation Between Anticholinergic Burden and Cognitive Functioning

We identified a negative correlation between measures of anticholinergic burden and the following MATRICS domains of cognition (Figure 2; see also Table S3 in the online supplement): global cognition (r=−0.37, 95% CI=−0.48, −0.25, Bonferroni-corrected p [p_{corr}]<0.001, I^2=68.2%), verbal learning (r=−0.28, 95% CI=−0.36, −0.21, p_{corr}<0.001, I^2=59.5%), visual learning (r=−0.17, 95% CI=−0.28, −0.06, p_{corr}=0.008, I^2=75.3%), working memory (r=−0.22, 95% CI=−0.29, −0.14, p_{corr}<0.001, I^2=66.6%), processing

FIGURE 1. PRISMA flow diagram for a study of anticholinergic burden and cognitive function in psychosis



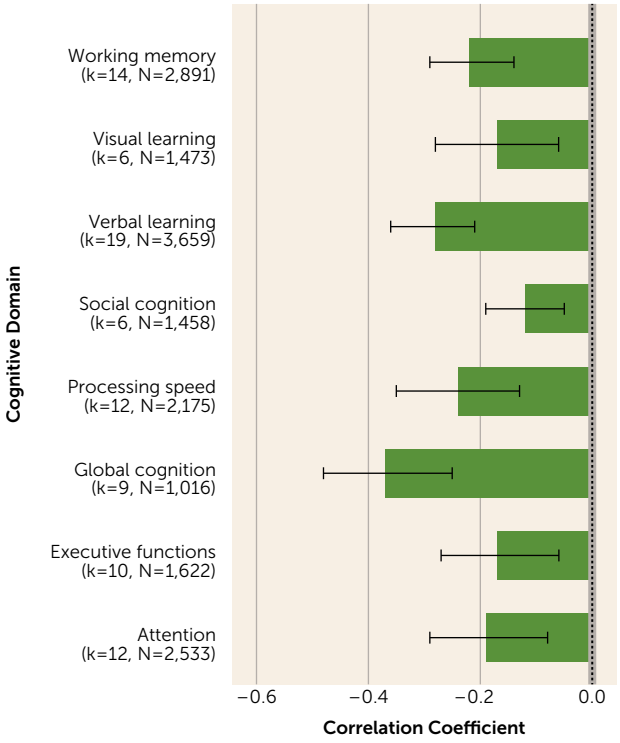
speed ($r=-0.24$, 95% CI=−0.35, −0.13, $p_{corr}<0.001$, $I^2=82.3\%$), attention ($r=-0.19$, 95% CI=−0.29, −0.08, $p_{corr}<0.01$, $I^2=54.6\%$), executive functions ($r=-0.17$, 95% CI=−0.27, −0.06, $p_{corr}<0.001$, $I^2=79.3\%$), and social cognition ($r=-0.12$, 95% CI=−0.19, −0.05, $p_{corr}=0.008$, $I^2=25.4\%$). Across all domains, there was no funnel plot asymmetry and Egger's test was not significant. (For individual forest and funnel plots for each cognitive domain, see Figure 3 and Figure S1 in the online supplement.)

We performed a sensitivity analysis excluding studies in which the anticholinergic burden was quantified as the dosage of anticholinergic medications rather than the cumulative anticholinergic burden arising from all medications taken by the patient. A negative correlation between anticholinergic burden and the following MATRICS domains of cognition remained apparent (see Figure S2 and Table S4 in the online supplement): global cognition ($r=-0.37$, 95% CI=−0.51, −0.23, $p_{corr}<0.001$, $I^2=75.6\%$), verbal learning ($r=-0.27$, 95% CI=−0.36, −0.18, $p_{corr}<0.001$, $I^2=82.4\%$), visual learning ($r=-0.17$, 95% CI=−0.3, −0.04, $p_{corr}=0.008$, $I^2=61.3$), working memory ($r=-0.22$, 95% CI=−0.29, −0.14, $p_{corr}<0.001$, $I^2=77.2\%$), processing speed ($r=-0.27$, 95% CI=−0.41, −0.14, $p_{corr}<0.001$, $I^2=84.4\%$), attention ($r=-0.17$, 95% CI=−0.3, −0.04, $p_{corr}<0.001$, $I^2=88.1\%$), executive functions ($r=-0.2$, 95% CI=−0.31, −0.1, $p_{corr}<0.001$, $I^2=68.3\%$), and social cognition ($r=-0.12$, 95% CI=−0.19, −0.04, $p_{corr}=0.008$, $I^2=75.9\%$).

We performed a second sensitivity analysis including only studies in which anticholinergic burden was estimated using the Anticholinergic Cognitive Burden scale. It was not possible to include visual learning, social cognition, and the global score of cognition because fewer than three studies were available. A negative correlation between anticholinergic burden and the following MATRICS domains of cognition remained apparent (see Figure S3 and Table S5 in the online supplement): verbal learning ($r=-0.17$, 95% CI=−0.23, −0.11, $p_{corr}=0.01$, $I^2=77.5\%$), working memory ($r=-0.19$, 95% CI=−0.24, −0.14, $p_{corr}=0.015$, $I^2=63.5\%$), processing speed ($r=-0.19$, 95% CI=−0.22, −0.15, $p_{corr}=0.01$, $I^2=20\%$), attention ($r=-0.18$, 95% CI=−0.25, −0.11, $p_{corr}=0.035$, $I^2=82.9\%$), and executive functions ($r=-0.17$, 95% CI=−0.20, −0.14, $p_{corr}=0.01$, $I^2=20\%$).

We performed a third sensitivity analysis including only studies (N=3) with individuals in a first episode of psychosis. Because the only cognitive domain available for all three studies was verbal learning, in this case we did not apply Bonferroni correction. A negative correlation between anticholinergic burden and verbal learning remained apparent in the subgroup of individuals with first-episode psychosis ($r=-0.29$, 95% CI=−0.46, −0.12, $p=0.013$, $I^2=82.4\%$; see Table S6 in the online supplement). We also tested the

FIGURE 2. Correlation values between anticholinergic burden and cognition for each cognitive domain[a]



[a] The mean r values across cognitive domains are given, along with the number of studies (k) and the number of participants included. Error bars indicate 95% confidence interval.

difference between the estimates of the meta-analysis of first-episode psychosis and the meta-analysis of individuals with a diagnosis of schizophrenia. The difference between the two estimates was not statistically significant ($z=-3.29$, $p=0.95$).

Correlation Between Serum Anticholinergic Activity and Cognitive Functioning

We identified a negative correlation between serological measures of anticholinergic burden and the following MATRICS domains of cognition (Figure 4; see also Table S7 in the online supplement): verbal learning ($r=-0.26$, 95% CI$=-0.38$, -0.14, $p_{corr}<0.001$, $I^2=19.4\%$), working memory ($r=-0.19$, 95% CI$=-0.35$, -0.03, $p_{corr}=0.03$, $I^2=51\%$), and executive functions ($r=-0.16$, 95% CI$=-0.27$, -0.04, $p_{corr}=0.03$, $I^2=11\%$). (For individual funnel plots for each cognitive domain, see Figure S4 in the online supplement.)

Effects of Anticholinergic Tapering or Challenge on Cognitive Functioning

Finally, tapering off anticholinergic medication improved the scores in the following MATRICS domains (Figure 5; see also Table S8 in the online supplement): verbal learning ($d=0.77$, 95% CI$=0.44$, 1.1, $p_{corr}=0.001$, $I^2=41.3\%$), working memory ($d=0.94$, 95% CI$=0.63$, 1.26, $p_{corr}=0.001$, $I^2=15.1\%$), and executive functions ($d=0.44$, 95% CI$=0.26$, 0.62, $p_{corr}=0.04$, $I^2=2.3\%$). Results for processing speed were not statistically significant ($d=1$, 93.8% CI$=-0.51$, 2.51, $p_{corr}>0.05$, $I^2=96$). (For individual funnel plots for each cognitive domain, see Figure S5 in the online supplement.)

We performed a sensitivity analysis excluding studies in which cognitive outcomes were measured before and after a challenge with an anticholinergic medication. Tapering off anticholinergic medication improved the scores in the following MATRICS domains (see Table S9 in the online supplement): verbal learning ($d=0.71$, 95% CI$=0.28$, 1.03, $p_{corr}=0.001$, $I^2=44.2$) and working memory ($d=0.96$, 95% CI$=0.61$, 1.32, $p_{corr}=0.001$, $I^2=20.7$). Results for processing speed were not statistically significant ($d=1.05$, 95% CI$=-1.08$, 3.18, $p_{corr}>0.05$, $I^2=96$). Results for executive functions are not reported, as all studies reporting this measure were tapering studies and the result therefore remains unchanged.

Quality Assessment

The quality rating of the studies according to the Newcastle-Ottawa Scale ranged from 3 to 9 (mean=6.7, median=7; see Table S10 in the online supplement).

Meta-Regressions

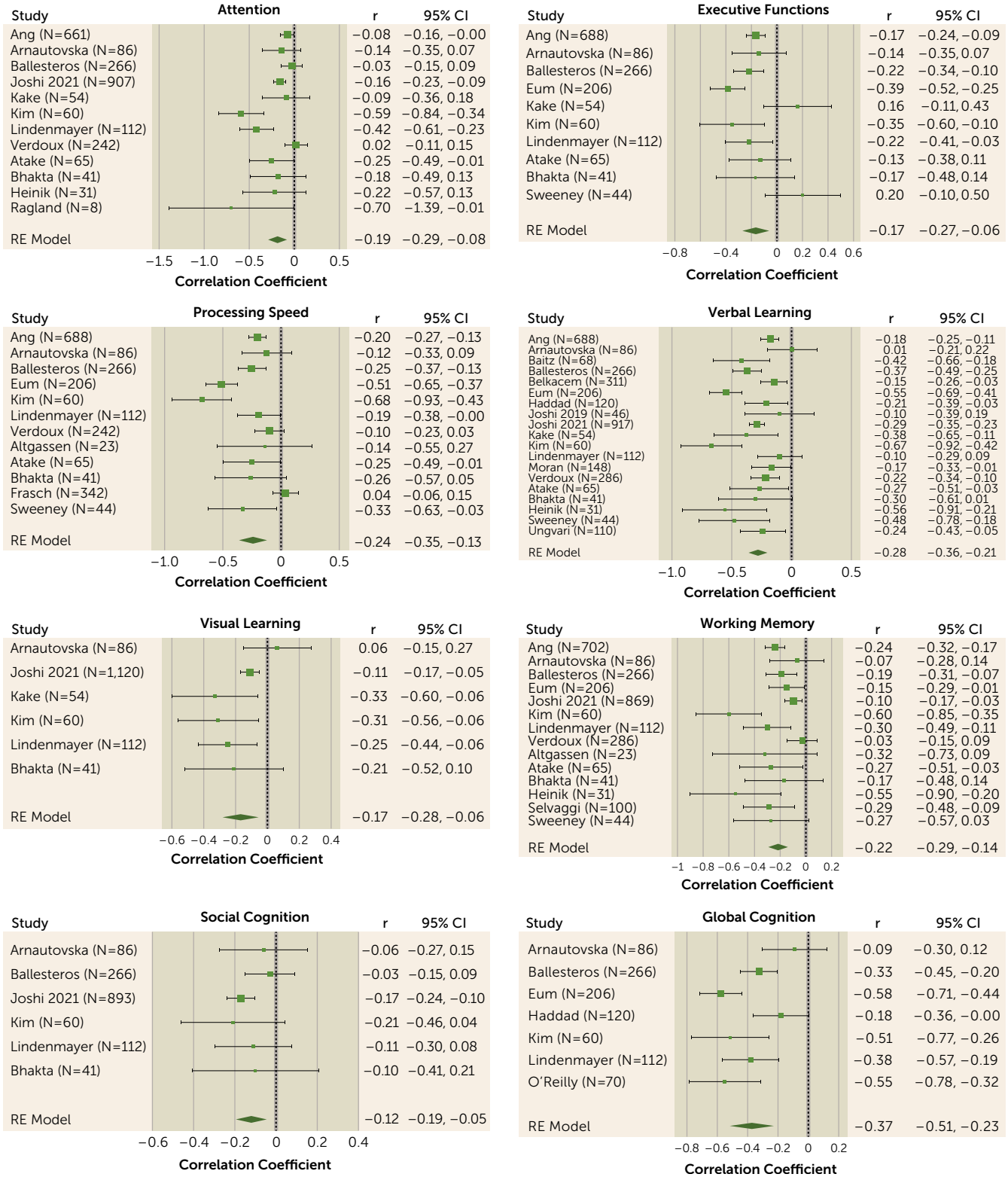
Meta-regressions were performed examining the association between effect sizes and age, sex, chlorpromazine-equivalent antipsychotic dosage, and scores from the Newcastle-Ottawa Scale. None of these analyses were statistically significant (see Table S11 in the online supplement).

DISCUSSION

In this systematic review and meta-analysis, we identified a robust association between greater anticholinergic medication burden and poorer cognitive function in individuals with psychosis. Regardless of the measure used to quantify anticholinergic burden, results consistently indicated lower cognitive functioning in patients with higher anticholinergic burden. The clinical relevance is further supported by the finding that reductions of anticholinergic burden in tapering studies were associated with significant improvements in cognitive function.

The association between anticholinergic burden and cognitive tests was largest for the global cognitive score, potentially reflecting the greater reliability of composite measures. We did not hypothesize a priori that any domain would be uniquely affected. Interestingly, among the individual cognitive domains investigated, verbal learning showed the greatest magnitude of effect. This finding is in line with preclinical studies showing a prominent role of the cholinergic system in facilitating learning. M1 receptor agonists have been shown to increase hippocampal neuronal firing (77) and to enhance novel object recognition (78) and spatial learning in mice (79). Similarly, in humans, the M1 allosteric agonist GSK1034702 improved episodic memory in tobacco smokers (80). Furthermore, xanomeline, an M1/M4 agonist, enhanced performance in various

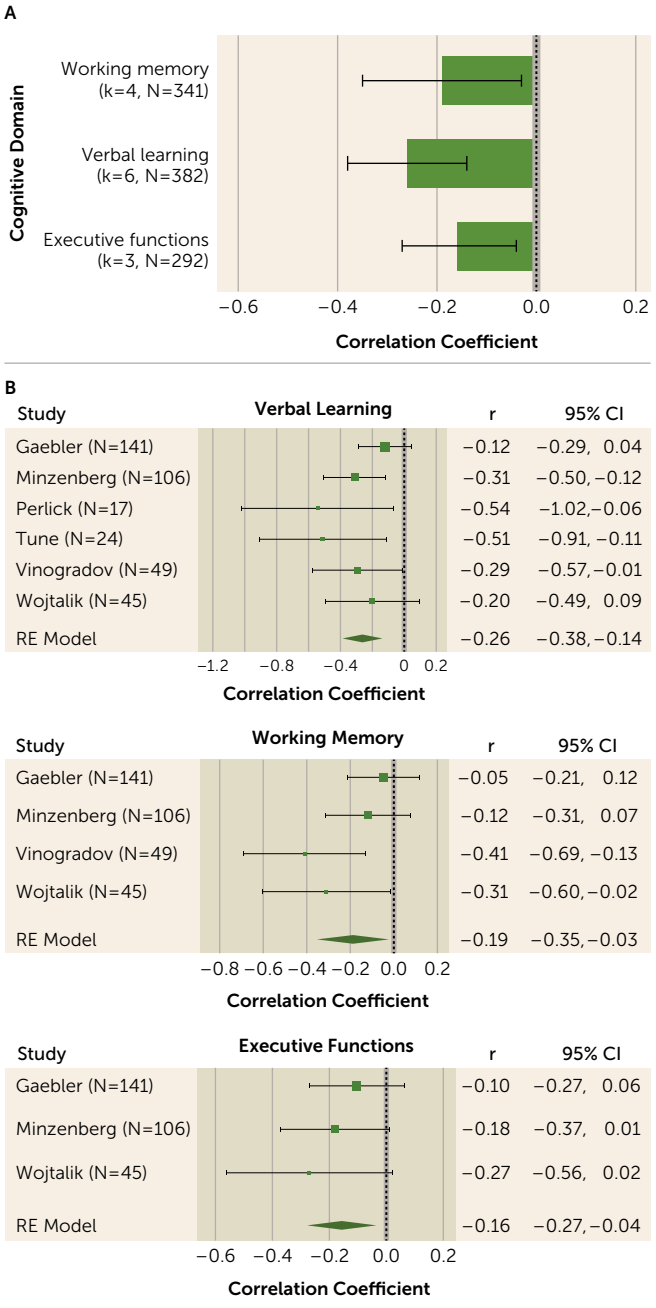
FIGURE 3. Forest plots of anticholinergic burden and each cognitive domain in single studies[a]



[a] The mean r values across cognitive domains are given for each study. Error bars indicate 95% confidence interval. RE model=random-effects model.

cognitive domains in people with psychosis, to a greater extent in verbal learning and working memory (16–18). Conversely, our findings revealed that social cognition was the domain least associated with anticholinergic burden. This is potentially related to the fact that social cognition is a higher-level function that involves long-term learning and is

FIGURE 4. Correlation values between serum anticholinergic activity and cognition for each cognitive domain[a]



[a] In panel A, the mean r values across cognitive domains are given, along with the number of studies (k) and the number of participants included. Panel B shows forest plots of single studies for each cognitive domain. Error bars indicate 95% confidence interval. RE model=random-effects model.

related to community functioning (81), and therefore may be less sensitive to pharmacological interventions. An alternative explanation is that social cognition scores were available for only a limited number of studies (N=6), potentially reducing the statistical power of this analysis.

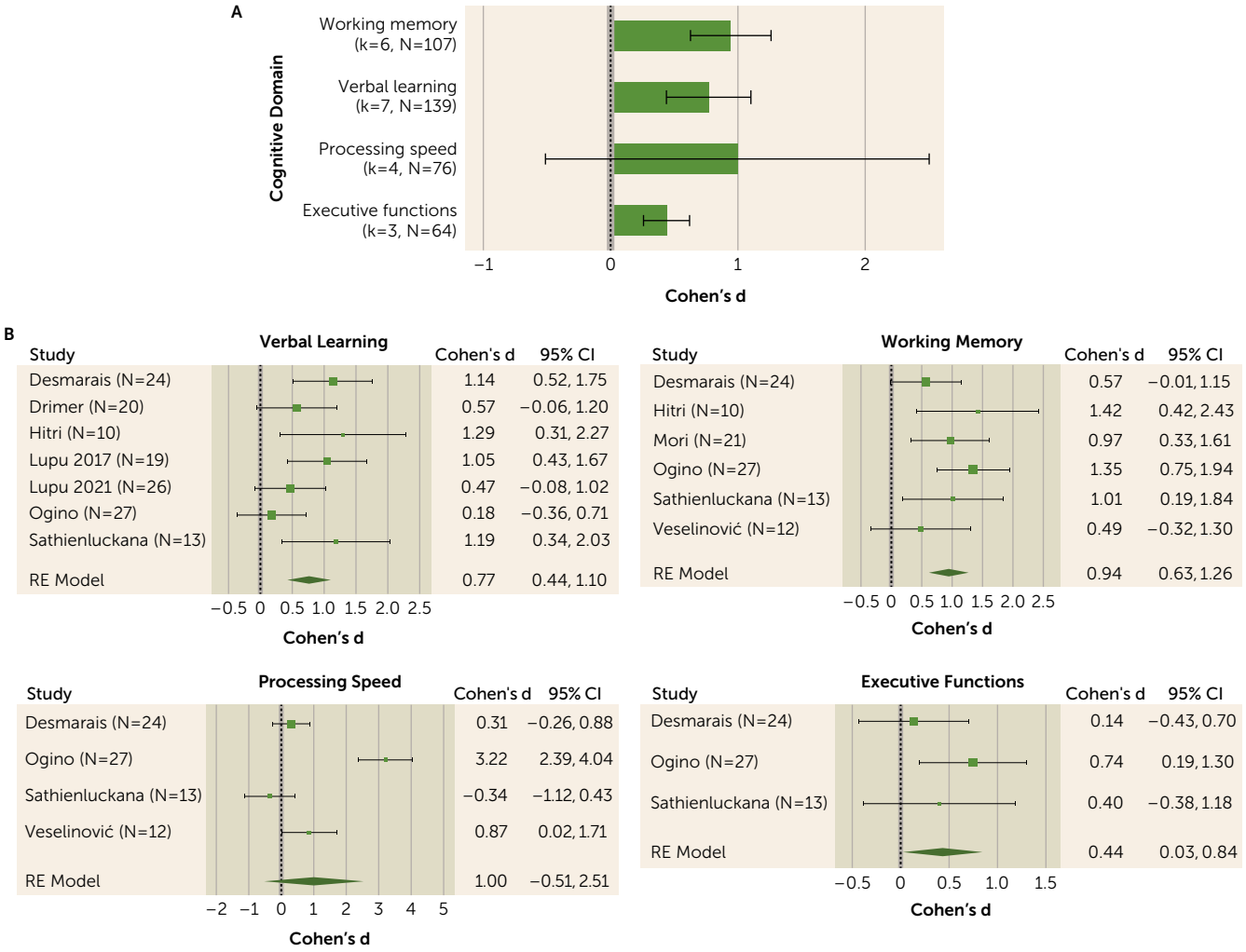
Our results suggest that the relationship between anticholinergic burden and cognitive function is similar in individuals with first-episode psychosis and those with a diagnosis of schizophrenia. While our findings demonstrate that anticholinergic burden may contribute to the cognitive impairments seen in psychosis regardless of the stage of psychosis, there is a wide range of additional contributing factors (6). Genetic, neurodevelopmental, environmental, and neurodegenerative factors all play a role across the course of psychotic illness (82–84). Therefore, the observed effect sizes likely reflect the complexity of cognitive impairment in psychosis, with anticholinergic burden accounting for a significant but not large proportion of the overall deficits. Anticholinergic burden, however, is of particular interest given that unlike many other risk factors for cognitive impairment, it is highly modifiable.

The World Health Organization recommends against prophylactic and long-term use of anticholinergic medications in people with psychosis (85). Despite this, anticholinergics are routinely prescribed for people with psychosis as a treatment for extrapyramidal side effects of antipsychotics (19). The present findings provide support for the hypothesis that reducing anticholinergic burden has procognitive effects. Cross-sectional findings, however, have the potential to be confounded. While the analysis of longitudinal studies did suggest benefits of reducing anticholinergic burden, these were unblinded studies with no control group, and it is possible that improvements in the cognitive tasks reflect practice effects. A randomized clinical trial design is necessary to control for practice effects of repeated cognitive testing.

This is the first meta-analysis to systematically examine the relationship between anticholinergic burden and cognitive functioning in psychosis. It included a large number of studies, showed no evidence of publication bias, and the findings have direct relevance to clinical practice. Several limitations should be noted, however. First, while the included studies were selected based on comparable validated cognitive scales, substantial methodological variability across studies remained. Similarly, the methods used to measure anticholinergic burden varied considerably across studies (i.e., various clinical scales and the dosage of anticholinergic medications). However, our sensitivity analysis showed that even after excluding studies that did not estimate the overall anticholinergic burden, results were comparable. Moreover, even including studies in which the anticholinergic burden was measured with the same scale (i.e., the Anticholinergic Cognitive Burden scale), the results were comparable. However, current measures for anticholinergic burden do not account for medication dosage. Given that there does appear to be a dose-related effect for anticholinergic drugs, the development of scales that account for this might improve the clinical relevance of these measures.

Second, we were not able to include in our analysis other variables that might be associated with cognitive impairment, such as the presence and degree of negative symptoms and depression and the overall burden of psychotic symptoms. Indeed, it is possible that individuals with greater

FIGURE 5. Effect of anticholinergic medication tapering on different cognitive domains[a]



[a] In panel A, mean Cohen's d values across cognitive domains are given, along with the number of studies (k) and the number of participants included. Panel B shows forest plots of single studies for each cognitive domain. Error bars indicate 95% confidence interval. RE model=random-effects model.

symptom severity are more likely to receive anticholinergic medications; however, with the present data it was not possible to test the consequence of this. Even for variables that were possible to include in the meta-regression, the lack of any significant relationship might reflect the fact that these analyses included only 10 to 20 studies and may therefore have been underpowered to detect a relationship. Furthermore, the lack of a relationship at the study level does not rule out a relationship at the clinically relevant level of the individual patient. This highlights the importance, in future studies investigating the link between anticholinergic burden and cognition, of thoroughly documenting and reporting all the potential confounding variables.

Third, the risk of bias of the included studies was rated as high in two studies, and moderate in 17 studies. Nonetheless, the risk of bias of most of the included studies was low (N=23).

Finally, some analyses, such as the correlation between serological anticholinergic activity and cognition and the examination of tapering effects, had limited statistical power due to the small number of included studies. The trials examining intervention were all within-subject designs without a control group to account for confounders such as practice effects. Randomized controlled studies would be of benefit to establish a causal relationship more definitively. Nonetheless, this meta-analysis represents the most comprehensive effort to date to systematically quantify the impact of anticholinergic burden on cognition in schizophrenia.

In summary, in this systematic review and meta-analysis, we found that anticholinergic burden is associated with worse cognitive functioning in patients with psychosis and that reducing anticholinergic medication was effective in improving cognitive function. These findings highlight the negative impact of routinely used pharmacological interventions on cognitive function in individuals with psychosis. From a clinical perspective, tapering off anticholinergic medication may be beneficial. However, further randomized

clinical trials are needed for an unbiased quantification of benefit.

AUTHOR AND ARTICLE INFORMATION

Department of Psychiatry (Mancini, Fanshawe, Varvari, Zauchenberger, Catalan, McGuire, McCutcheon), MRC Brain Network Dynamics Unit (Mancini), and Nuffield Department of Clinical Neurosciences, Wellcome Centre for Integrative Neuroimaging (Mancini), University of Oxford, Oxford, UK; TUNEUP, Oxford Health NHS Foundation Trust, Oxford, UK (Mancini, Varvari, Zauchenberger, McCutcheon); Department of Psychiatry, University of Geneva, Geneva (Latreche, McGinn); Oxford Health NHS Foundation Trust, Oxford, UK (Fanshawe, McGuire); Department of Psychosis Studies, Institute of Psychiatry, Psychology, and Neuroscience, King's College London (Catalan, Pillinger, McGuire, McCutcheon); Basurto University Hospital, OSI Bilbao-Basurto, Biobizkaia Health Research Institute, University of the Basque Country UPV/EHU, Centro de Investigación en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Bilbao, Spain (Catalan); South London and Maudsley NHS Foundation Trust, London (Pillinger).

Send correspondence to Dr. Mancini (valentina.mancini@ndcn.ox.ac.uk) and Dr. McCutcheon (robert.mccutcheon@psych.ox.ac.uk).

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