



The effect of scopolamine on memory and attention: a systematic review and meta-analysis

Title	The effect of scopolamine on memory and attention: a systematic review and meta-analysis
Author(s)	Miravalles, Cerena; Cannon, Dara M.; Hallahan, Brian
Publication Date	2025-04-08
Publisher	Cambridge University Press
Repository DOI	https://doi.org/10.1192/j.eurpsy.2025.2446

Review/Meta-analysis

Cite this article: Miravalles C, Cannon DM, Hallahan B (2025). The effect of scopolamine on memory and attention: a systematic review and meta-analysis. *European Psychiatry*, **68**(1), e50, 1–9

<https://doi.org/10.1192/j.eurpsy.2025.2446>

Received: 18 December 2024

Revised: 23 March 2025

Accepted: 30 March 2025

Keywords:

attention; cognition; memory; scopolamine; cholinergic system

Corresponding author:

Cerena Miravalles;

Email: c.miravalles1@universityofgalway.ie

The effect of scopolamine on memory and attention: a systematic review and meta-analysis

Cerena Miravalles^{1,2} , Dara M. Cannon²  and Brian Hallahan^{1,2} 

¹Clinical Research Facility, University of Galway, Galway, Ireland and ²Clinical Neuroimaging Laboratory, Centre for Neuroimaging and Cognitive Genomics, Galway Neuroscience Centre, College of Medicine, Nursing & Health Sciences, University of Galway, Galway, Ireland

Abstract

Background. Scopolamine is a muscarinic receptor antagonist and is widely utilized as a “memory-loss model.” However, its impact across different memory and attention tasks and using different modes of administration has yet to be clearly evaluated. This systematic review and meta-analysis investigates the effect of scopolamine, across all routes of administration and across different dosages, on memory and attention performance in healthy humans (PROSPERO ID: CRD42024531634).

Methods. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, we searched (on 20 April 2024) for studies that utilized scopolamine and assessed memory and/or attention. Random-effects meta-analyses were conducted across a range of memory and attention tasks using “Comprehensive Meta-Analysis,” Version 3, to evaluate differential pharmacological effects on cognitive tasks between the scopolamine and placebo groups.

Results. Forty-six studies fulfilled the inclusion and exclusion criteria. Scopolamine negatively impaired performance on all memory tasks (immediate memory, delayed recall, digit span, Buschke selective reminding task, and recognition memory) and led to slower reaction times for three of the five attention tasks examined (choice reaction time, simple reaction time, and rapid visual information processing) compared to placebo. Scopolamine’s negative effect on memory and attention was greater with injectable (e.g., intramuscular, intravenous, and subcutaneous) compared to non-injectable routes of administration (e.g., intranasal, oral, and transdermal).

Conclusion. This study supports the use of scopolamine as a “memory-loss model,” particularly when given by an injectable route of administration. Future clinical trials should evaluate the bioavailability of scopolamine across different routes of administration to ensure therapeutic benefits outweigh any potential adverse cognitive effects.

Introduction

Scopolamine, also known as hyoscine, is a tropane alkaloid and a nonselective, pan-muscarinic antagonist that acts as an inhibitor at muscarinic cholinergic receptor sites in the parasympathetic nervous system. Muscarinic cholinergic receptors, which recognize the neurotransmitter acetylcholine (ACh), are a family of seven-transmembrane domain receptors consisting of five receptor subtypes (M_{1-5}). Positron emission tomography (PET) studies exhibit scopolamine’s ability to occupy muscarinic cholinergic receptors in both human and nonhuman primates, demonstrating scopolamine’s involvement with the central nervous system (CNS) [1, 2]. Scopolamine induces peripheral and central antimuscarinic effects and is utilized for conditions that require decreased parasympathetic activity, including an antiemetic for motion sickness, post-operative nausea, and a sedative before anesthesia. Adverse effects related to anticholinergic activity are generally mild, but can include pupillary dilatation, tachycardia, decreased production of saliva and mucus, urinary retention, and potentially more rare and severe side effects such as hallucinations and delirium.

The cholinergic system in the human CNS comprised projections from the nuclei of the basal forebrain that innervate the hippocampus and most cortical regions, projections from the brainstem to the thalamus, and interneurons in the striatum and nucleus accumbens [3]. Many of these neuroanatomical areas are responsible for cognition, motor function, and affect [4]. Psychiatric disorders, including schizophrenia, and mood disorders, such as major depressive disorder (MDD) and bipolar disorder (BD), have been linked to dysregulation in the cholinergic system and dysfunction of cholinergic muscarinic receptors, specifically the M_1 and M_4 receptor for schizophrenia and the M_2 receptor for BD [5–10]. An increase of ACh in the CNS has been linked to an exacerbation of depressive symptoms and, conversely, a lack of ACh has been linked to (hypo)manic symptoms [11–13]. Consequently, a number of small randomized controlled

© The Author(s), 2025. Published by Cambridge University Press on behalf of European Psychiatric Association. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted re-use, distribution and reproduction, provided the original article is properly cited.



EUROPEAN PSYCHIATRIC ASSOCIATION

trials and a recent systematic review and meta-analysis demonstrated that scopolamine induces a rapid antidepressant effect in individuals experiencing a depressive episode in the context of either MDD or BD [14–19]. Potential adverse sequelae of scopolamine, including on various aspects of cognition, would be important to elucidate if scopolamine becomes a more widely used treatment intervention for the management of acute depressive episodes, particularly as such sequelae have not been examined in detail in treatment trials to date.

Scopolamine has additionally been noted in several studies to produce amnesic effects, likely related to its central anticholinergic activity, resulting in its use to induce memory impairment in healthy humans in studies involving a “memory-loss model” and in studies investigating treatments for dementia [20–39]. PET imaging in monkeys demonstrated impairment in working memory after scopolamine administration [2]. Studies that have explored the potential impact of scopolamine on memory and attention have focused predominantly on constructs, such as working, episodic, semantic, implicit, immediate, visual, long-term, or delayed recognition and verbal memory, as well as on retrieval, coding, and storage of information. While several studies have demonstrated amnesic effects, these findings have not been universally demonstrated, with several studies noting no significant impact on either memory [29, 31, 33, 35] or attention tasks [32, 34]. Variability in scopolamine’s effects may reflect individual differences, with CHRM2 genotype influencing inhibitory control and cholinergic pathways, potentially altering sensitivity to scopolamine-induced cognitive impairment [40]. Consequently, scopolamine’s validity as a model for cognitive dysfunction associated with dementia, including Alzheimer’s disease, has been questioned [41].

There are several factors that might influence the putative impact of scopolamine in relation to memory and attention. First, scopolamine can be administered via a range of different routes, all of which have different pharmacokinetic and metabolic profiles (Supplementary Table S1). Parenteral routes of administration, including intravenous (IV), subcutaneous (SC), and intramuscular (IM) routes, may produce more significant cognitive impairments pertaining to memory and attention [42–44], compared to oral (PO) and transdermal (TD) scopolamine administration [23, 45–47]. Second, higher dosages of scopolamine have been noted in some studies to induce more significant cognitive impairments, although there is limited data exploring if dosage across different modes of administration has a differential impact on performance in tasks pertaining to memory and attention [27, 44, 48].

Examining data systematically pertaining to the potential impact of scopolamine across different routes and dosages of administration in relation to a range of cognitive tasks assessing memory and attention will help inform clinicians of the risks and benefits of this medication, particularly given its continued use as a model of cognitive impairment and its potential future use as an agent with rapid antidepressant effects. Consequently, the aim of this systematic review and meta-analysis is to investigate the effects of scopolamine, across different routes of administration and across different dosages, compared to placebo in relation to its impact on a range of memory and attention performance tasks.

Methods

We conducted a systematic review that adhered to the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses

(PRISMA) checklist (Supplementary Table S2) [49] and preregistered our protocol (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=531634).

Eligibility criteria

We included human studies of healthy adult participants (≥ 18 years of age) to identify the impact of scopolamine administration via any mode of administration on cognitive tasks associated with both memory and attention. All included studies had a placebo arm and were written in English. Review articles, protocols, qualitative/case studies, open-label studies, research meeting abstracts, and conference presentations were excluded. In addition, studies including small sample sizes (≤ 6 individuals per study arm), where the impact of scopolamine was not possible to determine due to the concurrent administration of other study treatment(s) simultaneously, where the cognitive task included was conducted in less than three studies, or where studies were undertaken in unique environments (i.e., space craft and underwater) were excluded.

Search strategy

A database search was undertaken with no date restrictions applied, using Medline, Embase, PsychINFO, Web of Science, and the Clinical Trials (<https://www.clinicaltrials.gov/>) database. Relevant reviews and references of the included studies were searched manually to identify additional appropriate studies for this review. The search included the following medical subject key words: “((scopolamine) OR (hyoscine)) AND (cognition) OR (memory) OR (attention) OR (psychomotor) OR (emotion processing) OR (visual learning) OR (recall) OR (amnesia) OR (amnesic)).

Two authors (CM and BH) independently and blindly screened all the titles and abstracts against the eligibility criteria. Full texts of the remaining studies were assessed against the eligibility criteria (CM and BH), with any disagreements resolved through a discussion between these two authors.

Data extraction

CM extracted data from all the studies on 20 April 2024, with BH acting as a second blind rater. Any disagreements were resolved with discussion, with any unresolved differences discussed with DC. Effect measures, including mean and standard deviations, were reported as recorded by the study authors. Data extraction included relevant outcomes (observed effects of scopolamine on cognitive tasks), study characteristics (design including cognitive tasks employed, population, dose, and route of scopolamine), and clinical characteristics (population, sample size, age, sex, and education level).

Quality assessment

The Jadad scale [50] was used to assess the reliability and validity of studies. This tool assesses randomization, blinding, and study withdrawals on a 5-point scale. CM and BH independently and blindly completed the Jadad scale for all included studies, with any differences resolved with a discussion between the authors.

We assessed publication bias using funnel plots when 10 or more studies were included in the analysis. Funnel plots visually assess the symmetry of study effect sizes around the overall effect estimate. Symmetry suggests no significant publication bias, whereas asymmetry may indicate potential bias, such as missing studies with

nonsignificant results. For analyses with fewer than 10 studies, funnel plots were not used, as fewer studies reduce the statistical power needed to distinguish a true asymmetry from random variation [51].

Statistical analysis

A meta-analysis was conducted where three or more studies examined the impact of scopolamine compared to placebo for the same cognitive task. Effect sizes were calculated for continuous data by attaining the mean, standard deviations, and sample size of the scopolamine and placebo groups. When standard deviations were not available, these were estimated based on the other statistical parameters reported in the individual study. Standard errors (SEs) were converted to standard deviations as appropriate. When continuous data were not available, we evaluated dichotomous data and calculated the odds ratios, which were converted into Hedge's G effect size statistic (G). For studies using multiple arms of the drug and one arm of the placebo (e.g., different scopolamine doses compared with placebo), the " n " for the placebo group was divided by the number of strata in the study. Where sufficient data were available (≥ 3 studies), additional analyses were performed on "injection" (e.g., IV, IM, and SC) compared to "non-injection" (e.g., PO, TD, and

intranasal (IN)) routes of administration. Doses were categorized as "high" (≥ 0.5 mg) or "low" (< 0.5 mg). Age analysis grouped participants into "young" (18–40 years, mean age < 30 years) and "old" (> 40 years, mean age > 60 years) cohorts.

"Comprehensive Meta-Analysis," Version 3, evaluated differential medication effects on cognitive tasks between the scopolamine and placebo groups to ascertain the random-model treatment effect size (G), 95% confidence intervals (CIs), and SEs for each study [52]. Heterogeneity of interventions was assessed using the Cochrane Q and I^2 statistics, with significance determined at $p < 0.05$.

Results

Literature search

The PRISMA diagram summarizing the literature search strategy is presented in Figure 1. A total of 468 articles were identified, with 282 full texts reviewed and 106 studies included in the final analysis (eight from the reference lists). Studies were excluded if they lacked cognitive task data, involved open-label designs, used additional treatments, or had intervention arm sizes ≤ 6 participants. The sociodemographic and clinical characteristics of all included studies are provided in Supplementary Tables S3 and S4.

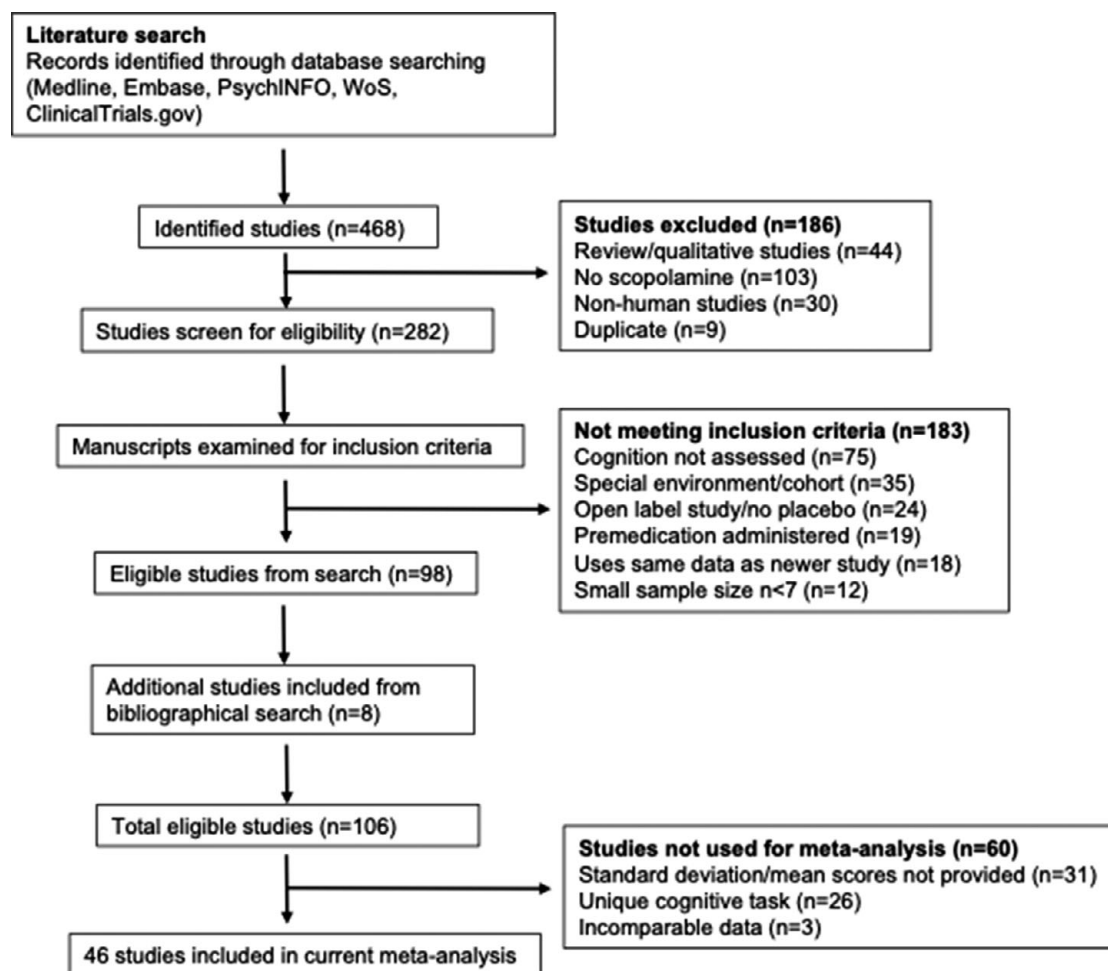


Figure 1. Flowchart describing the study selection process. List of unique cognitive tasks included in Supplementary Table S5.

Memory

Six different tasks provided data pertaining to performance and reaction time. Scopolamine significantly impaired memory performance and reaction time, only when scopolamine was administered via injection.

Free/immediate recall (Figure 2)

Twenty studies (35 strata; scopolamine $n = 493$, placebo $n = 492$) assessed free/immediate recall. Scopolamine impaired accuracy compared to placebo ($G = -0.86$, 95% CI: -1.08 to -0.64 , $p < 0.001$), with a significant effect in injection studies

($G = -1.00$, 95% CI: -1.25 to -0.76 , $p < 0.001$), but not in non-injection studies ($G = -0.16$, 95% CI: -0.70 to 0.38 , $p = 0.57$).

Post- versus pre-administration accuracy was lower in the scopolamine group ($G = -0.93$, 95% CI: -1.42 to -0.44 , $p < 0.001$), with insufficient studies present to examine injection and non-injection groups separately (Supplementary Figure S1). Scopolamine impaired performance at both high and low doses, with both the dose categories showing significant effects (Supplementary Figure S2). Evidence of publication or reporting bias, along with heterogeneity among the studies, was observed (Supplementary Figure S3). Performance was assessed 30 min–6 h post-administration, with no discernible impact of timing.

Free/Immediate Recall – Accuracy (% correct)

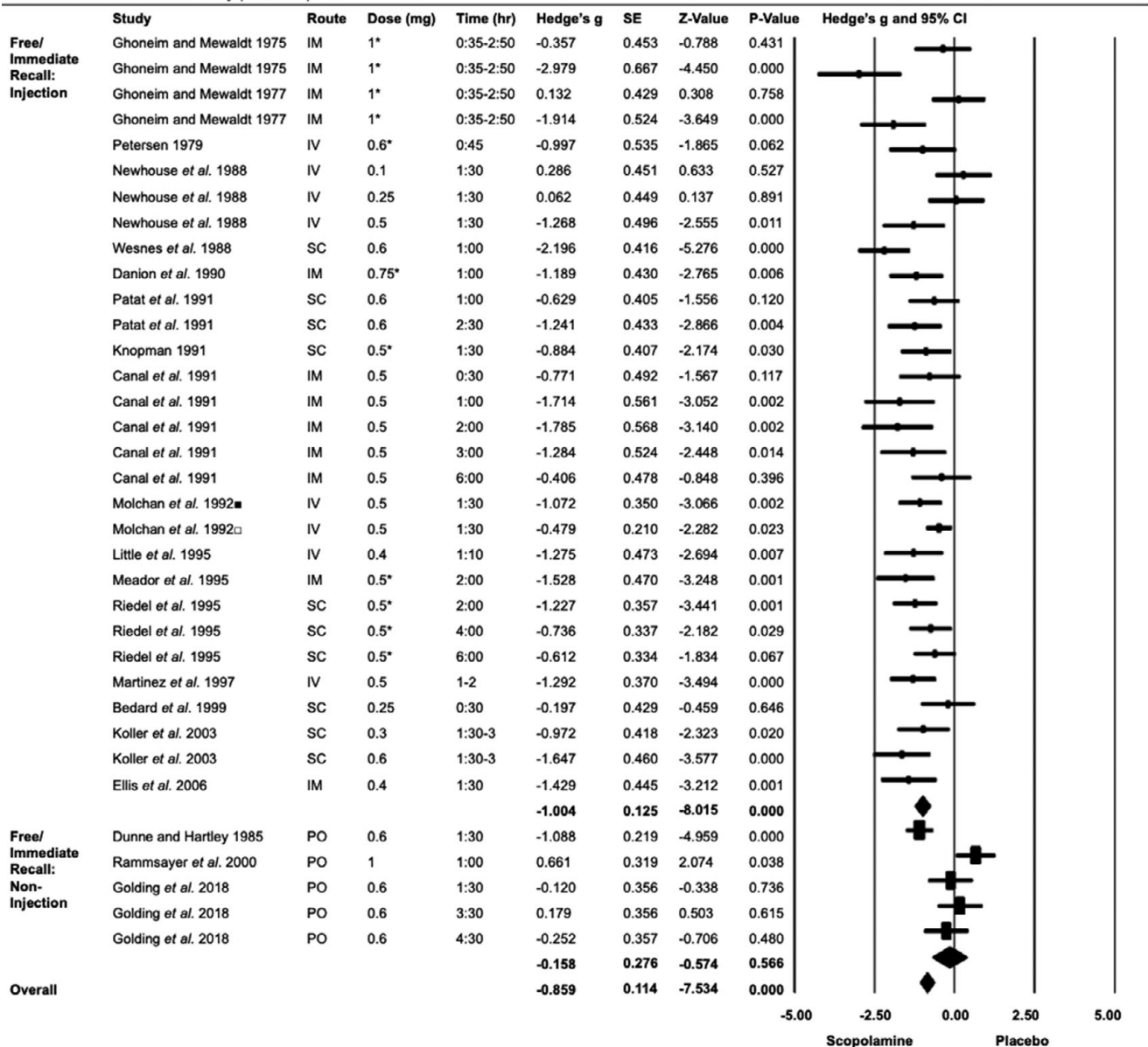


Figure 2. Free/immediate recall: accuracy (% correct).

■ Old cohort.

□ Young cohort.

IM, intramuscular; IV, intravenous; PO, oral; SC, subcutaneous.

*Studies that used microgram doses have been converted to milligrams based on a 75 kg body weight.

Delayed recall (Figure 3)

Fourteen studies (21 strata; scopolamine $n = 332$, placebo $n = 332$) utilized delayed recall, with scopolamine impairing performance compared to placebo ($G = -0.89$, 95% CI: -1.16 to -0.61 , $p < 0.001$). Both scopolamine injection ($G = -1.07$, 95% CI: -1.41 to -0.72 , $p < 0.001$) and non-injection ($G = -0.56$, 95% CI: -1.02 to -0.08 , $p = 0.018$) groups performed significantly worse compared to the placebo. Post-administration versus pre-administration accuracy showed no difference ($G = -0.29$, 95% CI: -1.08 to 0.50 , $p = 0.47$); however, three of the five strata included non-injectable scopolamine (Supplementary Figure S1). Scopolamine impaired performance at both high and low doses, with both the dose categories showing significant effects (Supplementary Figure S4). Evidence of publication or reporting bias was observed in the delayed recall task assessing performance (Supplementary Figure S5). This task was assessed 30 min–4.5 h post-administration, with no apparent impact of the timing.

Digit span (Supplementary Figure S6)

Thirteen studies (24 strata; scopolamine $n = 331$, placebo $n = 278$) assessed digit span forward, while four studies (10 strata; scopolamine $n = 157$, placebo $n = 119$) assessed digit span backward. Scopolamine had no overall effect on the digit span forward ($G = -0.158$, 95% CI: -0.42 to 0.11 , $p = 0.239$), although the injection group showed impairment ($G = -0.29$, 95% CI: -0.56 to -0.02 , $p = 0.034$). Scopolamine impaired the digit span backward performance compared to placebo ($G = -0.39$, 95% CI: -0.68 to -0.09 , $p = 0.011$). Comparing dose levels, digit span forward showed no

significant effect at either high or low doses, while scopolamine impaired the performance at high doses but not at low doses for digit span backward (Supplementary Figure S7). No evidence of publication or reporting bias was observed (Supplementary Figure S8). Performance was measured across a large time duration (30 min–70 h) post-scopolamine administration with no clear impact of timing.

Buschke selective reminding task (Supplementary Figure S9)

Ten studies examined accuracy utilizing the Buschke selective reminding task (16 strata; scopolamine $n = 225$, placebo $n = 173$), while five studies (10 strata; scopolamine $n = 137$, placebo $n = 85$) investigated consistency. The scopolamine group performed worse than placebo on both accuracy ($G = -1.13$, 95% CI: -1.43 to -0.83 , $p < 0.001$) and consistency tasks ($G = -1.33$, 95% CI: -1.8 to -0.86 , $p < 0.001$). Scopolamine also significantly impaired accuracy and consistency at both high and low doses (Supplementary Figure S10). Evidence of publication or reporting bias was observed in the delayed recall task assessing performance (Supplementary Figure S11). This task was assessed 55 min–2.5 h post-scopolamine administration, with no distinguishable impact of time evident.

Recognition memory (Supplementary Figure S12)

For the recognition memory task, eight studies (19 strata; scopolamine $n = 282$, placebo $n = 282$) examined accuracy, while five studies (12 strata; scopolamine $n = 208$, placebo $n = 208$) investigated the reaction time. Scopolamine significantly impaired both accuracy ($G = -0.43$, 95% CI: -0.73 to -0.14 , $p = 0.004$) and

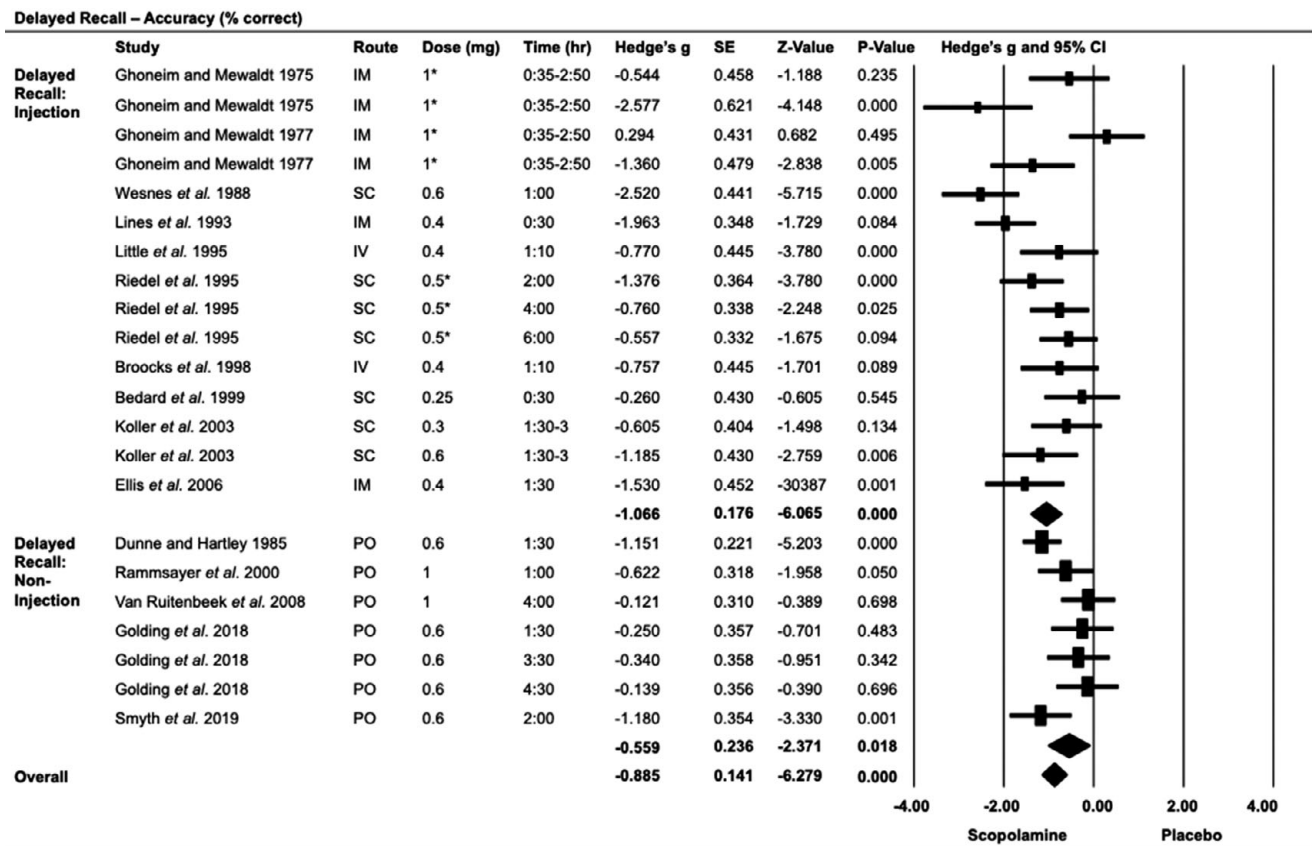


Figure 3. Delayed recall: accuracy (% correct).

IM, intramuscular; IV, intravenous; PO, oral; SC, subcutaneous.

*Studies that used microgram doses have been converted to milligrams based on a 75 kg body weight.

reaction time ($G = 0.19$, 95% CI: 0.001 to 0.37, $p = 0.048$) compared to the placebo group. High-dose scopolamine significantly impaired accuracy, while low-dose scopolamine had no effect (Supplementary Figure S13). This task was measured 30 min–4 h post-scopolamine administration, with no obvious impact of timing.

Sternberg memory scanning task (Supplementary Figure S14)

Four studies (five strata; scopolamine $n = 89$, placebo $n = 89$) utilized the Sternberg memory scanning task. Individuals in the scopolamine group performed worse on accuracy ($G = -0.82$, 95% CI: -1.27 to -0.38 , $p < 0.001$) and had slower reaction times ($G = 0.70$, 95% CI: 0.20 to 1.20, $p = 0.006$) compared to placebo. This task was measured across 55 min–3 h post-scopolamine administration, although no observable impact of time was evident.

Age and sex

Age analysis was conducted for free/immediate recall, digit span forward, and the Buschke selective reminding task (Supplementary Figures S15–S17). Scopolamine impaired both young and old cohorts in free/immediate recall and the Buschke selective reminding task, but only affected the young cohort in digit span forward. There were insufficient studies to conduct a meaningful sex analysis.

Attention

Five tasks provided measures of performance and reaction time. Scopolamine negatively impaired performance and significantly delayed reaction time during attention tasks, especially when post-administration scores were compared to baseline.

Choice reaction time (CRT) (Supplementary Figures S18–S21)

Twelve studies (27 strata; scopolamine $n = 423$, placebo $n = 385$) assessed reaction time, and four studies (eight strata; scopolamine $n = 131$, placebo $n = 93$) evaluated accuracy. The scopolamine group demonstrated a slower reaction time ($G = 0.80$, 95% CI: 0.48 to 1.13, $p < 0.001$), but not reduced accuracy ($G = -0.5$, 95% CI: -1.04 to 0.03, $p = 0.063$) compared to placebo. The effect size for a slower reaction time was larger for those who received scopolamine by injection ($G = 1.25$, 95% CI: 0.78 to 1.71, $p < 0.001$) compared to non-injectable scopolamine ($G = 0.39$, 95% CI: -0.06 to 0.84, $p = 0.091$). Comparing pre- to post-administration scores, seven studies (28 strata; scopolamine $n = 259$, placebo $n = 221$) investigated change in reaction time, and three studies (seven strata; scopolamine $n = 114$, placebo $n = 76$) examined change in accuracy. Scopolamine demonstrated slower reaction times ($G = 2.08$, 95% CI: 1.54 to 2.61, $p < 0.001$) and reduced accuracy ($G = -0.86$, 95% CI: -1.3 to -0.42 , $p < 0.001$) compared to placebo, with the injection group demonstrating slower reaction times. Scopolamine impaired reaction time at both high and low doses compared to placebo and worsened reaction time from pre- to post-administration (Supplementary Figures S22 and S23). This task was measured 45 min–70 h post-administration, with no impact of timing. Publication or reporting bias was evident for the CRT task assessing reaction time (Supplementary Figure S24). The adjusted values with the imputed studies reduced the effect size from $G = 0.83$ to $G = 0.64$ (95% CI: 0.21–1.08, $p = 0.004$).

Simple reaction time (SRT) (Supplementary Figures S19 and S21)

Eight studies (13 strata; scopolamine $n = 179$, placebo $n = 179$) utilized the SRT task. The scopolamine group showed slower reaction times ($G = 0.48$, 95% CI: 0.15 to 0.81, $p = 0.004$) compared

to placebo, with injectable administration demonstrating a larger effect size ($G = 0.85$, 95% CI: 0.22 to 1.56, $p = 0.008$) compared to the non-injection group ($G = 0.34$, 95% CI: -0.05 to 0.73, $p = 0.083$). Comparing pre- to post-administration scores, scopolamine was associated with slower reaction time ($G = 0.88$, 95% CI: 0.37 to 1.40, $p = 0.001$) compared to placebo. Comparing doses, scopolamine impaired reaction time at low doses but not at high doses (Supplementary Figure S25). Tasks ranged from 30 min to 4.5 h after scopolamine administration, with no apparent impact of time of administration.

Continuous performance task (CPT) (Supplementary Figure S19)

Four studies (10 strata; scopolamine $n = 115$, placebo $n = 117$) utilized the CPT (seven strata utilized an injectable mode of administration), with no significant effects of scopolamine compared to placebo. Measurements ranged from 1.5 to 70 h post-administration, with no impact of time of administration.

Rapid visual information processing (RVP) (Supplementary Figures S20 and S21)

Three studies (three strata (all injectable routes); scopolamine $n = 48$, placebo $n = 48$) utilized RVP. Examining change scores from baseline to post-scopolamine administration, scopolamine demonstrated slower reaction time ($G = -1.16$, 95% CI: -1.89 to -0.44 , $p = 0.002$) and less accuracy ($G = 1.74$, 95% CI: 1.28 to 2.21, $p < 0.001$) compared to placebo. This task was measured 1–2 h post-scopolamine administration, with no impact of time of administration.

Vigilance task (Supplementary Figure S18)

Three studies (five strata; scopolamine $n = 127$, placebo $n = 127$, three strata used an injectable mode of administration) utilized the vigilance task. No differential effects of scopolamine compared to placebo were noted for this task. This task was measured across 1–15.5 h post-scopolamine administration, with no impact of the time of administration.

Age and sex

There were too few studies to conduct a meaningful age or sex analysis for attention tasks.

Discussion

Scopolamine demonstrated a clear impairment for both memory and attention, particularly for tasks associated with working, episodic and recognition memory, and sustained attention utilizing this comprehensive systematic review and meta-analysis in healthy adults (Supplementary Tables S6 and S7). Similarly, scopolamine's adverse impact on memory and attention was greater with an injectable method of administration (e.g., IV, IM, and SC) compared to non-injectable routes (e.g., PO, TD, and IN).

Despite some previous divergent findings [41], we believe the results of this systematic review support scopolamine administration in an injectable format as a useful model for cognitive dysfunction and dementia, with delayed recall (a working memory task), for example, noted as impaired in early-stage Alzheimer's disease and clearly worsened by scopolamine administration [53, 54]. Furthermore, scopolamine-induced cognitive impairments are potentially relevant to understanding the cognitive deficits seen in schizophrenia, MDD and BD. The cholinergic system's role in these psychiatric disorders is underscored by our findings that

scopolamine can impact cognitive functions such as memory and attention, which are core components affected in these psychiatric disorders. These results not only support the hypothesis of cholinergic dysregulation in schizophrenia and MDD but also suggest that anticholinergic agents like scopolamine could potentially provide a valuable tool for investigating the neurochemical underpinnings of these conditions.

In comparison to placebo, scopolamine significantly impaired performance and consistency on the Buschke selective reminding test (Supplementary Figure S9), which evaluates the organization of long-term memory retrieval. Scopolamine also worsened performance and reaction times on the recognition memory (Supplementary Figure S12) and Sternberg tasks (Supplementary Figure S14), with the latter assessing working memory retrieval speed. While the digit span forward task (Supplementary Figure S6), a measure of working memory and attention, was not significantly affected, the scopolamine group did perform worse on this task. Scopolamine modestly impaired performance on the digit span backward task (Supplementary Figure S6), likely due to its lower difficulty compared to other working memory tasks (i.e., immediate and delayed recall) [55].

Similarly, the route of scopolamine administration affects its impact on cognitive performance in attention tasks. The injectable group exhibited slower reaction times on the CRT task compared to the non-injectable group (Supplementary Figure S19). The CRT task assesses sustained attention, and slower reaction times are indicative of poorer performance in attention tasks. Scopolamine also led to slower reaction times for both the SRT and RVP tasks (Supplementary Figure S21). Across all routes of administration, scopolamine negatively impacted performance on the CRT and RVP tasks compared to placebo (Supplementary Figure S20). There was no effect of scopolamine on the CPT and the vigilance task (Supplementary Figures S18 and S19); however, only three studies included these tasks, suggesting that the analysis may be underpowered to detect significant effects.

A likely rationale for the more significant cognitive deficits associated with injectable methods of scopolamine relate to its higher bioavailability with 100% absorption into the blood stream (half-life ~68.7 min) for IV scopolamine compared to 13% bioavailability (half-life ~63.7 min) for PO administration and even slower delivery for TD administration of (>4 h) [56]. PET imaging utilizing [¹¹C] scopolamine further supports this by demonstrating that IV administration enables rapid CNS penetration and significant receptor occupancy, reflecting high bioavailability [1]. Therefore, methods with higher bioavailability, such as injectables, consequently have a greater impact on memory and attention than lower bioavailability.

The varied timing of task administration in this meta-analysis complicates conclusions about scopolamine's impact on cognition. Cognitive deficits were observed as early as 1 h post-administration, but studies assessing memory 30–45 min post-administration found no significant effects [22, 41, 57, 58], and adverse effects were minimal after 6 h. For instance, free/immediate recall was unaffected after 6 h [28, 31], and digit span forward displayed no deficits compared to placebo at 22, 46, and 72 h [23]. Similarly, the CRT task displayed no effect on reaction time 30 min post-administration [59], with negligible effects for attention tasks evident after 11 h [23, 46]. These results should also be considered in the context of differing pharmacokinetic profiles associated with the route of administration. For example, injectable scopolamine achieves rapid systemic availability and peak effects, potentially explaining the early cognitive deficits observed, while PO or TD administration produces a slower onset of action with more sustained plasma

concentrations. Consequently, although scopolamine, particularly when administered via injectable methods, impacts cognition, these effects are not long-lasting. This is of particular importance given the potential benefit IV scopolamine may impart for individuals experiencing a depressive episode [14, 15, 18].

Higher doses of scopolamine consistently impaired memory and attention, while lower doses also produced significant deficits in several tasks, particularly free/immediate recall, delayed recall, and CRT reaction time. However, some tasks, such as digit span forward, were unaffected, and in certain cases (e.g., digit span backward, recognition memory, and SRT reaction time), impairments were observed only at high or low doses, suggesting task-specific dose sensitivity. In addition, physiological factors such as body weight and gender may impact scopolamine's pharmacokinetics. As scopolamine is highly lipid soluble, facilitating its redistribution into fatty tissues, gender (i.e., women generally have a higher fat content than men with a similar body mass index) and body weight may result in different distribution and clearance rates of scopolamine. Further research should consider body weight, sex differences, and other physiological variables. In addition, microgram doses have been converted to milligrams based on a 75 kg body weight for 11 studies, which potentially adds confounding variation to the analyses. While this approach helps standardize dosing, we acknowledge its limitations, as it may not fully account for individual differences in body composition and metabolism.

This study has other limitations. Older studies (pre-2000) had lower quality scores based on the Jadad rating scale, although all included trials were randomized and double-blinded [50]. Several studies fulfilling the inclusion criteria also had to be excluded due to insufficient extractable data. In addition, fewer studies evaluated certain memory and attention tasks, making comparisons between injectable and non-injectable administration methods unfeasible for some tasks. Moreover, an inadequate number of individual studies restricted the analysis of evidence for publication or reporting bias. However, where possible, consistency and precision across effects were examined.

In conclusion, this systematic review and meta-analysis, the largest to date investigating scopolamine's effect on cognition in a healthy population, provides evidence of scopolamine's negative effects on both memory and attention, with cognitive impairment more significant via injectable compared to non-injectable routes of administration. Despite scopolamine's long-established use in medical practice, notable gaps persist in our understanding of its pharmacological impacts, especially its potential as a rapid antidepressant. Given the preliminary evidence supporting scopolamine's use in treating depressive episodes, additional randomized controlled trials are suggested to determine optimal dosages and administration methods that maximize antidepressant benefits while minimizing adverse effects. Future clinical trials should evaluate the bioavailability of scopolamine across different routes of administration, to ensure its therapeutic benefits outweigh any potential adverse cognitive effects.

Supplementary material. The supplementary material for this article can be found at <http://doi.org/10.1192/j.eurpsy.2025.2446>.

Data availability statement. Data are available upon request.

Author contribution. Cerena Miravalles and Brian Hallahan designed the study. Cerena Miravalles conducted the bibliographical literature searches and the statistical analyses. Cerena Miravalles, Brian Hallahan and Dara M. Cannon drafted and revised the manuscript. All authors have agreed on the final manuscript and the decision to submit for publication.

Financial support. This work was supported by the Hardiman Scholarship, awarded by the University of Galway.

Competing interests. All authors report no financial interests or any potential conflicts of interest.

References

- [1] Frey KA, Koeppe RA, Mulholland GK, Jewett D, Hichwa R, Ehrenkaufer RL, et al. In vivo muscarinic cholinergic receptor imaging in human brain with [¹¹C]scopolamine and positron emission tomography. *J Cereb Blood Flow Metab.* 1992;12(1):147–54.
- [2] Yamamoto S, Nishiyama S, Kawamata M, Ohba H, Wakuda T, Takei N, et al. Muscarinic receptor occupancy and cognitive impairment: a PET study with [¹¹C](+)-3-MPB and scopolamine in conscious monkeys. *Neuropsychopharmacology.* 2011;36(7):1455–65.
- [3] Everitt BJ, Robbins TW. Central cholinergic systems and cognition. *Annu Rev Psychol.* 1997;48:649–84.
- [4] Scarr E, Gibbons AS, Neo J, Udawela M, Dean B. Cholinergic connectivity: it's implications for psychiatric disorders. *Front Cell Neurosci.* 2013;7:55.
- [5] Gibbons AS, Scarr E, McLean C, Sundram S, Dean B. Decreased muscarinic receptor binding in the frontal cortex of bipolar disorder and major depressive disorder subjects. *J Affect Disord.* 2009;116(3):184–91.
- [6] Cannon DM, Carson RE, Nugent AC, Eckelman WC, Kiesewetter DO, Williams J, et al. Reduced muscarinic type 2 receptor binding in subjects with bipolar disorder. *Arch Gen Psychiatry.* 2006;63(7):741–7.
- [7] Cannon DM, Klaver JK, Gandhi SK, Solorio G, Peck SA, Erickson K, et al. Genetic variation in cholinergic muscarinic-2 receptor gene modulates M2 receptor binding in vivo and accounts for reduced binding in bipolar disorder. *Mol Psychiatry.* 2011;16(4):407–18.
- [8] Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct Funct.* 2008;213(1–2):93–118.
- [9] Vaidya S, Guerin AA, Walker LC, Lawrence AJ. Clinical effectiveness of muscarinic receptor-targeted interventions in neuropsychiatric disorders: a systematic review. *CNS Drugs.* 2022;36(11):1171–206.
- [10] Kaul I, Sawchak S, Correll CU, Kakar R, Breier A, Zhu H, et al. Efficacy and safety of the muscarinic receptor agonist KarXT (xanomeline-trospium) in schizophrenia (EMERGENT-2) in the USA: results from a randomised, double-blind, placebo-controlled, flexible-dose phase 3 trial. *Lancet.* 2024;403(10422):160–70.
- [11] Janowsky DS, el-Yousef K, Davis JM, Sekerke HJ. Parasympathetic suppression of manic symptoms by physostigmine. *Arch Gen Psychiatry.* 1973;28(4):542–7.
- [12] Janowsky DS, el-Yousef MK, Davis JM. Acetylcholine and depression. *Psychosom Med.* 1974;36(3):248–57.
- [13] Janowsky DS, el-Yousef MK, Davis JM, Sekerke HJ. A cholinergic-adrenergic hypothesis of mania and depression. *Lancet.* 1972;2(7778):632–5.
- [14] Furey ML, Drevets WC. Antidepressant efficacy of the antimuscarinic drug scopolamine: a randomized, placebo-controlled clinical trial. *Arch Gen Psychiatry.* 2006;63(10):1121–9.
- [15] Drevets WC, Furey ML. Replication of scopolamine's antidepressant efficacy in major depressive disorder: a randomized, placebo-controlled clinical trial. *Biol Psychiatry.* 2010;67(5):432–8.
- [16] Janowsky DS. Serendipity strikes again: scopolamine as an antidepressant agent in bipolar depressed patients. *Curr Psychiatry Rep.* 2011;13(6):443–5.
- [17] Ellis JS, Zarate CA, Jr., Luckenbaugh DA, Furey ML. Antidepressant treatment history as a predictor of response to scopolamine: clinical implications. *J Affect Disord.* 2014;162:39–42.
- [18] McCaffrey U, Cannon DM, Hallahan B. The muscarinic-cholinergic system as a target in the treatment of depressive or manic episodes in bipolar disorder: a systematic review and meta-analysis. *J Affect Disord Rep.* 2021;6:100235.
- [19] Khajavi D, Farokhnia M, Modabbernia A, Ashrafi M, Abbasi SH, Tabrizi M, et al. Oral scopolamine augmentation in moderate to severe major depressive disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry.* 2012;73(11):1428–33.
- [20] Sunderland T, Tariot PN, Cohen RM, Weingartner H, Mueller 3rd, EA, Murphy DL. Anticholinergic sensitivity in patients with dementia of the Alzheimer type and age-matched controls. A dose-response study. *Arch Gen Psychiatry.* 1987;44(5):418–26.
- [21] Broks P, Preston GC, Traub M, Poppleton P, Ward C, Stahl SM. Modelling dementia: effects of scopolamine on memory and attention. *Neuropsychologia.* 1988;26(5):685–700.
- [22] Kopelman MD, Corn TH. Cholinergic 'blockade' as a model for cholinergic depletion. A comparison of the memory deficits with those of Alzheimer-type dementia and the alcoholic Korsakoff syndrome. *Brain.* 1988;111(Pt 5):1079–110.
- [23] Brazell C, Preston GC, Ward C, Lines CR, Traub M. The scopolamine model of dementia: chronic transdermal administration. *J Psychopharmacol.* 1989;3(2):76–82.
- [24] Wesnes K, Anand R, Lorscheid T. Potential of moclobemide to improve cerebral insufficiency identified using a scopolamine model of aging and dementia. *Acta Psychiatr Scand Suppl.* 1990;360:71–2.
- [25] Patat A, Klein MJ, Surjus A, Hucher M, Granier J. RU 41,656 does not reverse the scopolamine-induced cognitive deficit in healthy volunteers. *Eur J Clin Pharmacol.* 1991;41(3):225–31.
- [26] Knopman D. Unaware learning versus preserved learning in pharmacologic amnesia: similarities and differences. *J Exp Psychol Learn Mem Cogn.* 1991;17(5):1017–29.
- [27] Curran HV, Schifano F, Lader M. Models of memory dysfunction? A comparison of the effects of scopolamine and lorazepam on memory, psychomotor performance and mood. *Psychopharmacology (Berl).* 1991;103(1):83–90.
- [28] Canal N, Franceschi M, Alberoni M, Castiglioni C, De Moliner P, Longoni A. Effect of L-alpha-glyceryl-phosphorylcholine on amnesia caused by scopolamine. *Int J Clin Pharmacol Ther Toxicol.* 1991;29(3):103–7.
- [29] Molchan SE, Martinez RA, Hill JL, Weingartner HJ, Thompson K, Vitiello B, et al. Increased cognitive sensitivity to scopolamine with age and a perspective on the scopolamine model. *Brain Res Brain Res Rev.* 1992;17(3):215–26.
- [30] Schifano F, Curran HV. Pharmacological models of memory dysfunction? A comparison of the effects of scopolamine and lorazepam on word valence ratings, priming and recall. *Psychopharmacology (Berl).* 1994;115(3):430–4.
- [31] Riedel W, Hogervorst E, Lebourg R, Verhey F, van Praag H, Jolles J. Caffeine attenuates scopolamine-induced memory impairment in humans. *Psychopharmacology (Berl).* 1995;122(2):158–68.
- [32] Brass EP, Polinsky R, Sramek JJ, Moore M, Jones D, Veroff AE, et al. Effects of the cholinomimetic SDZ ENS-163 on scopolamine-induced cognitive impairment in humans. *J Clin Psychopharmacol.* 1995;15(1):58–62.
- [33] Duka T, Ott H, Rohloff A, Voet B. The effects of a benzodiazepine receptor antagonist beta-carboline ZK-93426 on scopolamine-induced impairment on attention, memory and psychomotor skills. *Psychopharmacology (Berl).* 1996;123(4):361–73.
- [34] Tariot PN, Patel SV, Cox C, Henderson RE. Age-related decline in central cholinergic function demonstrated with scopolamine. *Psychopharmacology (Berl).* 1996;125(1):50–6.
- [35] Martinez R, Molchan SE, Lawlor BA, Thompson K, Martinson H, Latham G, et al. Minimal effects of dextroamphetamine on scopolamine-induced cognitive impairments in humans. *Biol Psychiatry.* 1997;41(1):50–7.
- [36] Brooks A, Little JT, Martin A, Minichiello MD, Dubbert B, Mack C, et al. The influence of ondansetron and m-chlorophenylpiperazine on scopolamine-induced cognitive, behavioral, and physiological responses in young healthy controls. *Biol Psychiatry.* 1998;43(6):408–16.
- [37] Liem-Moolenaar M, Zoethout RW, de Boer P, Schmidt M, de Kam ML, Cohen AF, et al. The effects of a glycine reuptake inhibitor R231857 on the central nervous system and on scopolamine-induced impairments in cognitive and psychomotor function in healthy subjects. *J Psychopharmacol.* 2010;24(11):1681–7.
- [38] Blin O, Audebert C, Pitel S, Kaladjian A, Casse-Perrot C, Zaim M, et al. Effects of dimethylaminoethanol pyroglutamate (DMAE p-Glu) against

- memory deficits induced by scopolamine: evidence from preclinical and clinical studies. *Psychopharmacology (Berl)*. 2009;207(2):201–12.
- [39] Reches A, Levy-Cooperman N, Laufer I, Shani-Hershkovitch R, Ziv K, Kerem D, et al. Brain Network Activation (BNA) reveals scopolamine-induced impairment of visual working memory. *J Mol Neurosci*. 2014;54(1):59–70.
- [40] Zink N, Bensmann W, Arning L, Stock AK, Beste C. CHRM2 genotype affects inhibitory control mechanisms during cognitive flexibility. *Mol Neurobiol*. 2019;56(9):6134–41.
- [41] Flicker C, Ferris SH, Serby M. Hypersensitivity to scopolamine in the elderly. *Psychopharmacology (Berl)*. 1992;107(2–3):437–41.
- [42] Ebert U, Siepmann M, Oertel R, Wesnes KA, Kirch W. Pharmacokinetics and pharmacodynamics of scopolamine after subcutaneous administration. *J Clin Pharmacol*. 1998;38(8):720–6.
- [43] Ebert U, Grossmann M, Oertel R, Gramatte T, Kirch W. Pharmacokinetic-pharmacodynamic modeling of the electroencephalogram effects of scopolamine in healthy volunteers. *J Clin Pharmacol*. 2001;41(1):51–60.
- [44] Sannita WG, Maggi L, Rosadini G. Effects of scopolamine (0.25–0.75 mg i. m.) on the quantitative EEG and the neuropsychological status of healthy volunteers. *Neuropsychobiology*. 1987;17(4):199–205.
- [45] Parrott AC. The effects of transdermal scopolamine and four dose levels of oral scopolamine (0.15, 0.3, 0.6, and 1.2 mg) upon psychological performance. *Psychopharmacology (Berl)*. 1986;89(3):347–54.
- [46] Gordon C, Binah O, Attias J, Rolnick A. Transdermal scopolamine: human performance and side effects. *Aviat Space Environ Med*. 1986;57(3):236–40.
- [47] Bukala BR, Browning M, Cowen PJ, Harmer CJ, Murphy SE. Overnight transdermal scopolamine patch administration has no clear effect on cognition and emotional processing in healthy volunteers. *J Psychopharmacol*. 2019;33(2):255–7.
- [48] Newhouse PA, Sunderland T, Tariot PN, Weingartner H, Thompson K, Mellow AM, et al. The effects of acute scopolamine in geriatric depression. *Arch Gen Psychiatry*. 1988;45(10):906–12.
- [49] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev*. 2021;10(1):89.
- [50] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1–12.
- [51] Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. 2011;343:d4002.
- [52] Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. *Comprehensive meta-analysis (version 3)*. Englewood, NJ: Biostat; 2014.
- [53] Cerami C, Dubois B, Boccardi M, Monsch AU, Demonet JF, Cappa SF, et al. Clinical validity of delayed recall tests as a gateway biomarker for Alzheimer's disease in the context of a structured 5-phase development framework. *Neurobiol Aging*. 2017;52:153–66.
- [54] Welsh K, Butters N, Hughes J, Mohs R, Heyman A. Detection of abnormal memory decline in mild cases of Alzheimer's disease using CERAD neuropsychological measures. *Arch Neurol*. 1991;48(3):278–81.
- [55] Mintzer MZ, Griffiths RR. Differential effects of scopolamine and lorazepam on working memory maintenance versus manipulation processes. *Cogn Affect Behav Neurosci*. 2007;7(2):120–9.
- [56] Renner UD, Oertel R, Kirch W. Pharmacokinetics and pharmacodynamics in clinical use of scopolamine. *Ther Drug Monit*. 2005;27(5):655–65.
- [57] Bedard MA, Pillon B, Dubois B, Duchesne N, Masson H, Agid Y. Acute and long-term administration of anticholinergics in Parkinson's disease: specific effects on the subcortico-frontal syndrome. *Brain Cogn*. 1999;40(2):289–313.
- [58] Petersen RC. Scopolamine state-dependent memory processes in man. *Psychopharmacology (Berl)*. 1979;64(3):309–14.
- [59] Vitiello B, Martin A, Hill J, Mack C, Molchan S, Martinez R, et al. Cognitive and behavioral effects of cholinergic, dopaminergic, and serotonergic blockade in humans. *Neuropsychopharmacology*. 1997;16(1):15–24.