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

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ABSTRACT

BACKGROUND: Scopolamine is a muscarinic receptor antagonist and widely utilised as a "memory-loss model." However, its impact across different memory and attention tasks and using different modes of administration have 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).

MEHTHODS: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, we searched (20th April 2024) for studies that utilised 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 scopolamine and placebo groups.

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

Keywords: scopolamine, cognition, memory, attention

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INTRODUCTION

Scopolamine, also known as hyoscine, is a tropane alkaloid and a non-selective, pan-muscarinic antagonist that acts as an inhibitor at muscarinic cholinergic receptor sites in the parasympathetic nervous system. Muscarinic cholinergic receptors, which recognise 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 non-human primates, demonstrating scopolamine's involvement with the central nervous system (CNS) [1, 2]. Scopolamine induces peripheral and central antimuscarinic effects and is utilised for conditions that require decreased parasympathetic activity including an antiemetic for motion sickness, post-operative nausea, and a sedative prior to anaesthesia. 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 central nervous system is comprised of projections from the nuclei of the basal forebrain that innervate the hippocampus and most cortical regions, projections from brainstem to 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 and bipolar disorder 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 bipolar disorder [5-10]. An increase of acetylcholine in the central nervous system has been linked to an exacerbation of depressive symptoms and conversely a lack of acetylcholine has been linked to (hypo)manic symptoms [11-13]. Consequently, a number of small randomised controlled 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

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context of either major depressive or bipolar disorder [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 amnestic 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. Whilst several studies have demonstrated amnestic 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. Firstly, scopolamine can be administered via a range of different routes, all of which have different pharmacokinetic and metabolic profiles (Table S1). Parenteral routes of administration including intravenous, subcutaneous and intramuscular routes, may produce more significant cognitive impairments pertaining to memory and attention [42-44], compared to oral and transdermal scopolamine administration [23, 45-47]. Secondly, higher dosages of scopolamine have been noted in some studies to induce more

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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 which adhered to the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses (PRISMA) checklist (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. Additionally, 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 3 studies, or

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where studies were undertaken in unique environments (i.e. space craft, underwater) were excluded.

Search Strategy

A database search was undertaken with no date restrictions applied, using Medline, Embase, PsychINFO, Web of Science (WoS) and the Clinical Trials (https://www.clinicaltrials.gov/) database. Relevant reviews and references of 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 eligibility criteria (CM and BH) with any disagreements resolved through discussion between these two authors.

Data Extraction

CM extracted data from all the studies on April 20th, 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, education level).

Quality Assessment

The Jadad scale [50], was used to assess the reliability and validity of studies. This tool assesses randomisation, blinding, and study withdrawals on a 5-point scale. CM and BH

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151 independently and blindly completed the Jadad scale for all included studies with any
152 differences resolved with discussion between the authors.

153 We assessed publication bias using funnel plots when 10 or more studies were
154 included in the analysis. Funnel plots visually assess the symmetry of study effect sizes
155 around the overall effect estimate. Symmetry suggests no significant publication bias, whereas
156 asymmetry may indicate potential bias, such as missing studies with non-significant results.
157 For analyses with fewer than 10 studies, funnel plots were not used, as fewer studies reduce
158 the statistical power needed to distinguish true asymmetry from random variation [51].

159

160 **Statistical Analysis**

161 A meta-analysis was conducted where three or more studies examined the impact of
162 scopolamine compared to placebo for the same cognitive task. Effect sizes were calculated
163 for continuous data by attaining the mean, standard deviations and sample size of the
164 scopolamine and placebo groups. When standard deviations were not available, these were
165 estimated based on the other statistical parameters reported in the individual study. Standard
166 errors were converted to standard deviations as appropriate. When continuous data were not
167 available, we evaluated dichotomous data, calculated odds ratios which were converted into
168 the Hedge's G effect size statistic (G). For studies using multiple arms of the drug and one
169 arm of the placebo (e.g., different scopolamine doses compared with placebo), the "*n*" for the
170 placebo group was divided by the number of strata in the study. Where sufficient data was
171 available (≥3 studies), additional analyses were performed on "injection" (e.g., intravenous,
172 intramuscular, subcutaneous) compared to "non-injection" (e.g., oral, transdermal, intranasal)
173 routes of administration. Doses were categorized as "high" (≥0.5 mg) or "low" (<0.5 mg). Age
174 analysis grouped participants into "young" (18–40 years, mean age <30) and "old" (>40 years,
175 mean age >60) cohorts.

176 "Comprehensive Meta-Analysis," Version 3 evaluated differential medication effects on
177 cognitive tasks between the scopolamine and placebo groups to ascertain the random-model
178 treatment effect size (G), 95% confidence intervals (CI), and standard errors (SE) for each

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study [52]. Heterogeneity of interventions were assessed using the Cochrane Q, and I^2 statistics, with significance determined at $p < 0.05$.

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RESULTS

Literature Search

The PRISMA diagram summarising 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 (8 from 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 socio-demographic and clinical characteristics of all included studies are provided in Table S3 & S4.

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

1. *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- vs. 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 (Figure S1). Scopolamine impaired performance at both high and low doses, with both dose categories showing significant effects (Figure S2). Evidence of publication or reporting bias, along with heterogeneity among the studies, was observed

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(Figure S3). Performance was assessed 30 minutes to 6 hours post-administration, with no discernible impact of timing.

2. *Delayed Recall* (Figure 3)

Fourteen studies (21 strata; scopolamine n = 332, placebo n = 332) utilised 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 placebo. Post-administration vs. 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 (Figure S1). Scopolamine impaired performance at both high and low doses, with both dose categories showing significant effects (Figure S4). Evidence of publication or reporting bias was observed in the delayed recall task assessing performance (Figure S5). This task was assessed 30 minutes to 4.5 hours post-administration, with no apparent impact of the timing.

3. *Digit Span* (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 digit span forward (G = -0.158, 95% CI -0.42 to 0.11, p = 0.239), though the injection group showed impairment (G = -0.29, 95% CI -0.56 to -0.02, p = 0.034). Scopolamine impaired 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 performance at high doses but not low doses for digit span backward (Figure S7). No evidence of publication or reporting bias was observed (Figure S8). Performance was measured across a large time-duration (30 minutes to 70 hours) post-scopolamine administration with no clear impact of timing.

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243 *4. Buschke Selective Reminding Task* (Figure S9)

244 Ten studies examined accuracy utilising the Buschke Selective Reminding Task, (16 strata;
245 scopolamine *n* = 225, placebo *n* = 173), while 5 studies (10 strata; scopolamine *n* = 137,
246 placebo *n* = 85) investigated consistency. The scopolamine group performed worse than
247 placebo on both accuracy (G = -1.13, 95% CI -1.43 to -0.83, $p < 0.001$) and consistency tasks
248 (G = -1.33, 95% CI -1.8 to -0.86, $p < 0.001$). Scopolamine also significantly impaired accuracy
249 and consistency at both high and low doses (Figure S10). Evidence of publication or reporting
250 bias was observed in the delayed recall task assessing performance (Figure S11). This task
251 was assessed 55 minutes to 2.5 hours post-scopolamine administration with no
252 distinguishable impact of time evident.

253

254 *5. Recognition Memory* (Figure S12)

255 For the recognition memory task, eight studies (19 strata; scopolamine *n* = 282, placebo *n* =
256 282) examined accuracy while five studies (12 strata; scopolamine *n* = 208, placebo *n* = 208)
257 investigated reaction time. Scopolamine significantly impaired both accuracy (G = -0.43, 95%
258 CI -0.73 to -0.14, $p = 0.004$) and reaction time (G = 0.19, 95% CI 0.001 to 0.37, $p = 0.048$)
259 compared to the placebo group. High-dose scopolamine significantly impaired accuracy, while
260 low-dose scopolamine had no effect (Figure S13). This task was measured 30 minutes to 4
261 hours post scopolamine administration, with no obvious impact of timing.

262

263 *6. Sternberg Memory Scanning Task* (Figure S14)

264 Four studies (5 strata; scopolamine *n* = 89, placebo *n* = 89) utilised the Sternberg memory
265 scanning task. Individuals in the scopolamine group performed worse on accuracy (G = -0.82,
266 95% CI -1.27 to -0.38, $p < 0.001$) and had slower reaction times (G = 0.70, 95% CI 0.20 to
267 1.20, $p = 0.006$) compared to placebo. This task was measured across 55 minutes to 3 hours
268 post-scopolamine administration, although no observable impact of time was evident.

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Age and Sex

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

[*Figure 2 here*]

Figure 2. Free/Immediate Recall – Accuracy (% correct)
■ Old cohort.
□ Young cohort.
PO = oral, IM = intramuscular, IV = intravenous, SC = subcutaneous
*Studies that used microgram doses have been converted to milligrams based off a 75kg body weight.

[*Figure 3 here*]

Figure 3. Delayed Recall – Accuracy (% correct)
PO = oral, IM = intramuscular, IV = intravenous, SC = subcutaneous
*Studies that used microgram doses have been converted to milligrams based off a 75kg body weight.

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.

1. *Choice Reaction Time (CRT)* (Figures S18-S21)

Twelve studies (27 strata; scopolamine n = 423, placebo n = 385) assessed reaction time, and four studies (8 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

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placebo. The effect size for a slower reaction time was larger for those who received scopolamine by injection (G = 1.25, CI 0.78 to 1.71, p < 0.001) compared to non-injectable scopolamine (G = 0.39, 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 (7 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 (Figure S22 & S23). This task was measured 45 minutes to 70 hours post-administration with no impact of timing. Publication or reporting bias was evident for the CRT task assessing reaction time (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 to 1.08, *p* = 0.004).

2. *Simple Reaction Time (SRT)* (Figures S19 and S21)

Eight studies (13 strata; scopolamine *n* = 179, placebo *n* = 179) utilised 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 (Figure S25). Tasks ranged from 30 minutes to 4.5 hours post scopolamine administration with no apparent impact of time of administration.

3. *Continuous Performance Task (CPT)* (Figure S19)

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Four studies (10 strata; scopolamine *n* = 115, placebo *n* = 117) utilised the CPT (7 strata utilised an injectable mode of administration), with no significant effects of scopolamine compared to placebo. Measurements ranged from 1.5 to 70 hours post-administration, with no impact of time of administration.

4. Rapid Visual Information Processing (RVP) (Figures S20 and S21)

Three studies (3 strata (all injectable routes); scopolamine *n* = 48, placebo *n* = 48) utilised 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 to 2 hours post scopolamine administration with no impact of time of administration.

5. Vigilance Task (Figure *S*18)

Three studies (5 strata; scopolamine *n* = 127, placebo *n* = 127, 3 strata used an injectable mode of administration) utilised the vigilance task. No differential effects of scopolamine compared to placebo were noted for this task. This task was measured across 1 to 15.5 hours 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 utilising this comprehensive systematic review and meta-analysis in healthy adults (Tables S6 & S7). Similarly, scopolamine's adverse impact on memory and attention was greater with an

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injectable method of administration (e.g., IV, IM, SC) compared to non-injectable routes (e.g., PO, TD, 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 (Figure S9), which evaluates the organisation of long-term memory retrieval. Scopolamine also worsened performance and reaction times on the Recognition Memory (Figure S12) and Sternberg tasks (Figure S14), with the latter assessing working memory retrieval speed. While the Digit Span Forward Task (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 (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 (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 (Figures

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S21). Across all routes of administration, scopolamine negatively impacted performance on the CRT and RVP tasks compared to placebo (Figure S20). There was no effect of scopolamine on the CPT and the Vigilance Task (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 minutes) for IV scopolamine compared to 13% bioavailability (half-life ~63.7 minutes) for oral administration and even slower delivery for transdermal administration of (> 4 hours) [56]. PET imaging utilising [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 one-hour post-administration, but studies assessing memory 30-45 mins post-administration found no significant effects [22, 41, 57, 58], and adverse effects were minimal after six hours. For instance, Free/Immediate Recall was unaffected after 6 hours [28, 31], and Digit Span Forward displayed no deficits compared to placebo at 22, 46, and 72 hours [23]. Similarly, the CRT task displayed no effect on reaction time 30 mins post-administration [59], with negligible effects for attention tasks evident after 11 hours [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 oral or transdermal 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

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416 importance given the potential benefit IV scopolamine may impart for individuals experiencing
417 a depressive episode [14, 15, 18].

418 Higher doses of scopolamine consistently impaired memory and attention, while lower
419 doses also produced significant deficits in several tasks, particularly Free/Immediate Recall,
420 Delayed Recall, and CRT reaction time. However, some tasks, such as Digit Span Forward,
421 were unaffected, and in certain cases (e.g., Digit Span Backward, Recognition Memory, and
422 SRT reaction time), impairments were observed only at high or low doses, suggesting task-
423 specific dose sensitivity. Additionally, physiological factors such as body weight and gender
424 may impact scopolamine's pharmacokinetics. As scopolamine is highly lipid soluble,
425 facilitating its redistribution into fatty tissues, gender (i.e. women generally have a higher fat
426 content than men with a similar body mass index) and body weight may result in different
427 distribution and clearance rates of scopolamine. Further research should consider body
428 weight, sex differences, and other physiological variables. Additionally, microgram doses have
429 been converted to milligrams based off a 75kg body weight for eleven studies which potentially
430 add confounding variation to the analyses. While this approach helps standardise dosing, we
431 acknowledge its limitations, as it may not fully account for individual differences in body
432 composition and metabolism.

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

441 In conclusion, this systematic review and meta-analysis, the largest to date
442 investigating scopolamine's effect on cognition in a healthy population, provides evidence of
443 scopolamine's negative effects on both memory and attention with cognitive impairment more

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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 randomised controlled trials are suggested to determine optimal dosages and administration methods that maximise antidepressant benefits while minimising 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.

AUTHOR CONTRIBUTIONS

C.M. and B.H. designed the study. C.M. conducted the bibliographical literature searches and the statistical analyses. C.M., B.H. and D.M.C drafted and revised the manuscript. All authors have agreed on the final manuscript and the decision to submit for publication.

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COMPETING INTERESTS

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

DATA AVAILABILITY

Data available upon request.

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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, Dara M. Cannon, and Brian Hallahan. The muscarinic-cholinergic system as a target in the treatment of depressive or manic episodes in bipolar disorder: A systematic review and meta-analysis. Journal of Affective Disorders Reports. 2021;6.
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.

https://doi.org/10.1192/j.eurpsy.2025.2446 Published online by Cambridge University Press

20. Sunderland T, Tariot PN, Cohen RM, Weingartner H, Mueller EA, 3rd, 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, Leboux 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. Broocks 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

https://doi.org/10.1192/j.eurpsy.2025.2446 Published online by Cambridge University Press

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, L. V., Higgins, J. P. T., & Rothstein, H. R. 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.

https://doi.org/10.1192/j.eurpsy.2025.2446 Published online by Cambridge University Press

632 58. Petersen RC. Scopolamine state-dependent memory processes in man.
633 Psychopharmacology (Berl). 1979;64(3):309-14.
634 59. Vitiello B, Martin A, Hill J, Mack C, Molchan S, Martinez R, et al. Cognitive and
635 behavioral effects of cholinergic, dopaminergic, and serotonergic blockade in humans.
636 Neuropsychopharmacology. 1997;16(1):15-24.
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638

https://doi.org/10.1192/j.eurpsy.2025.2446 Published online by Cambridge University Press

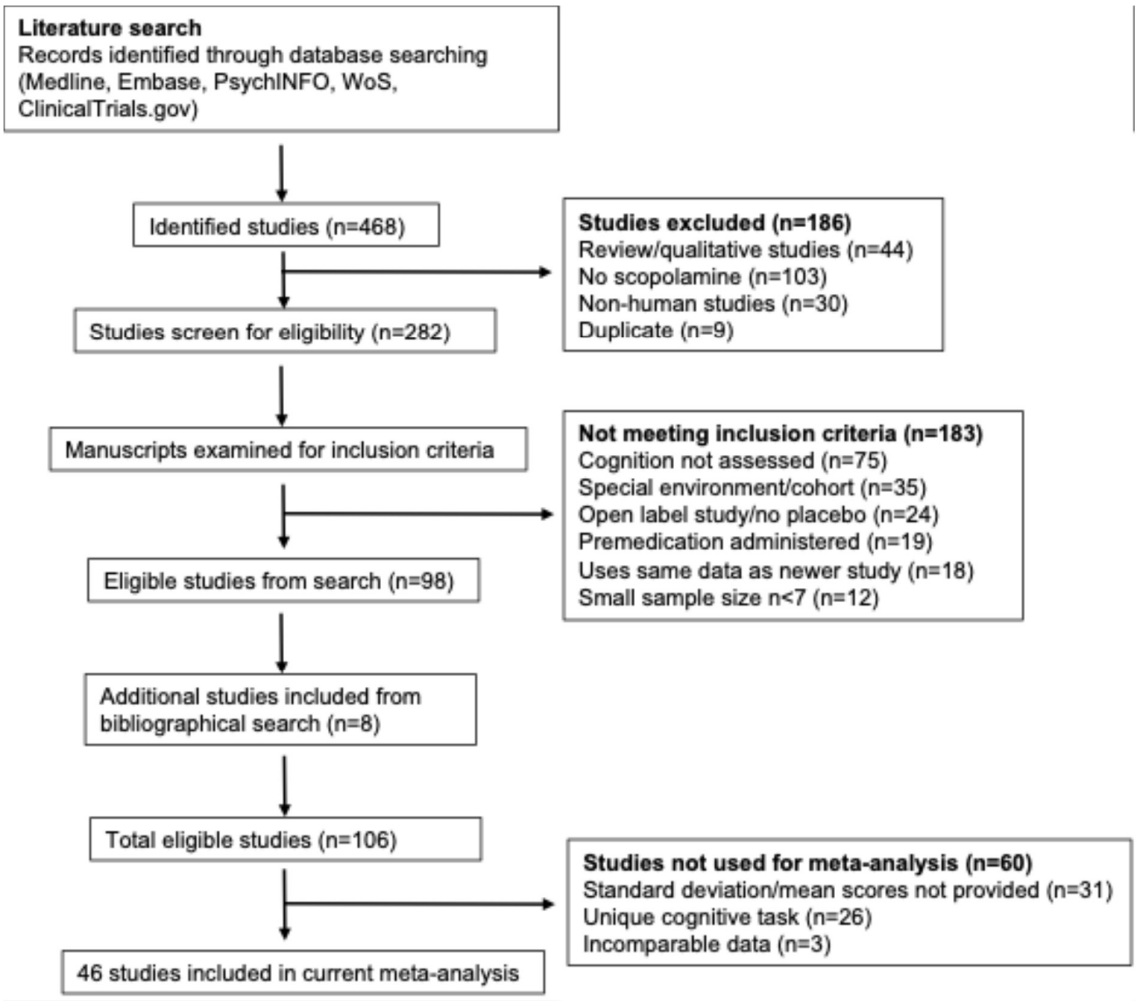

Figure 1. Flowchart describing the study selection process.
List of unique cognitive tasks included in Table S5

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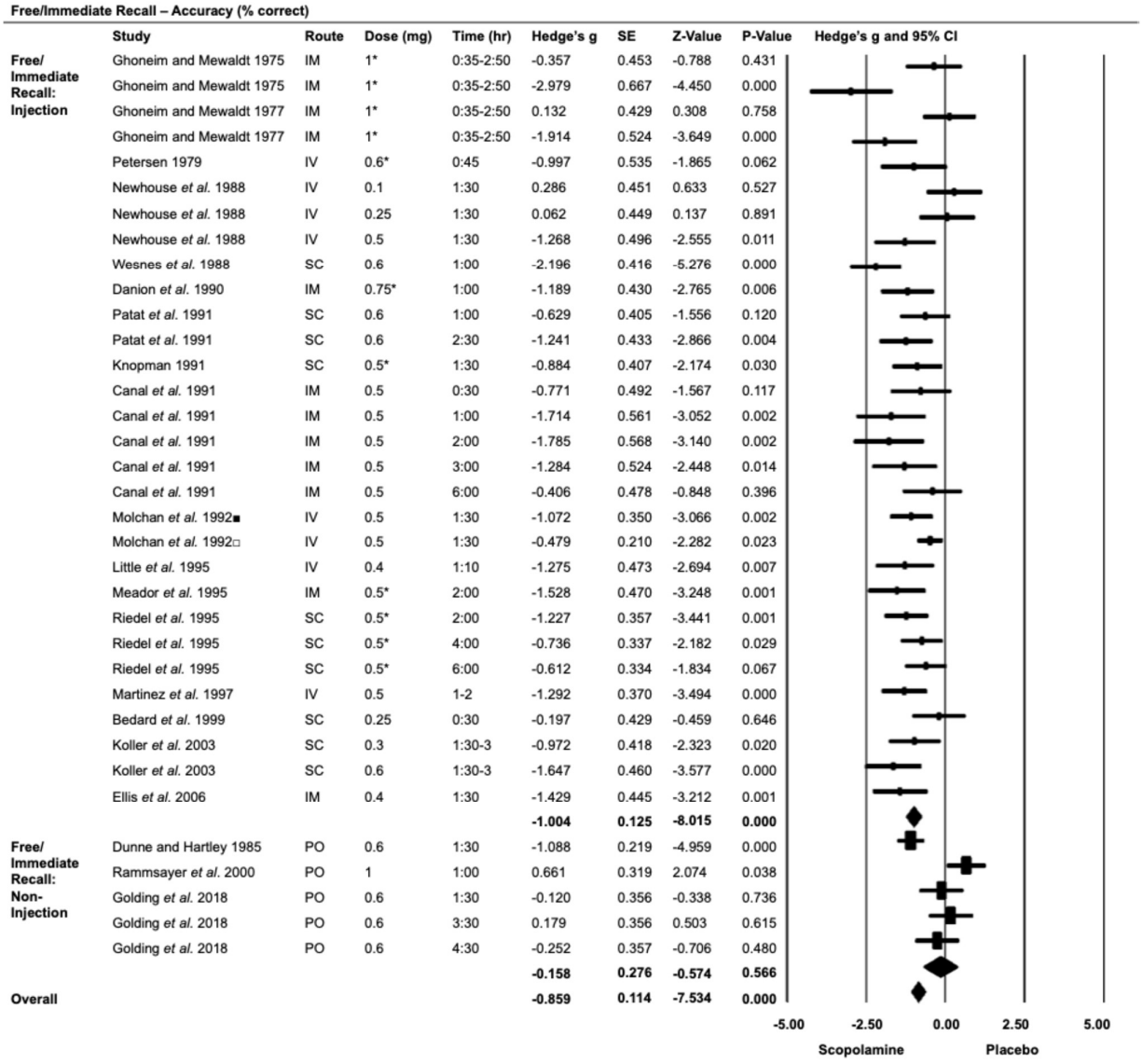

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644 **Figure 2.** Free/Immediate Recall – Accuracy (% correct)

645 ■ Old cohort.

646 □ Young cohort.

647 PO = oral, IM = intramuscular, IV = intravenous, SC = subcutaneous

648 *Studies that used microgram doses have been converted to milligrams based off a 75kg

649 body weight.

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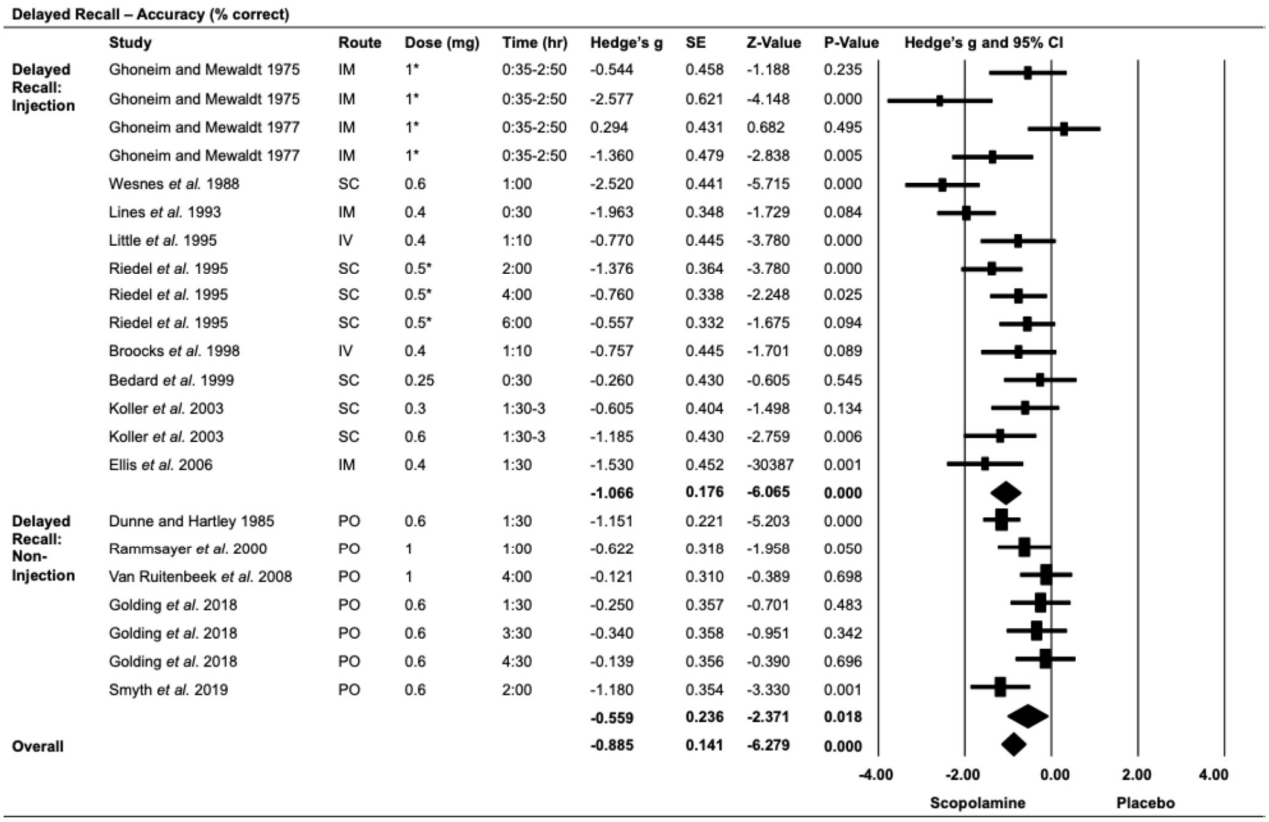

Figure 3. Delayed Recall – Accuracy (% correct)
PO = oral, IM = intramuscular, IV = intravenous, SC = subcutaneous
*Studies that used microgram doses have been converted to milligrams based off a 75kg body weight.

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