A Randomized Controlled Trial of Intravenous Scopolamine Versus Active-Placebo Glycopyrrolate in Patients With Major Depressive Disorder

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ABSTRACT

Objective: To investigate scopolamine's rapid-acting antidepressant effects using an active placebo comparator. Most prior intravenous scopolamine studies reduced depressive symptomatologies compared to saline placebo infusions within 3 days. However, the confounding effect of placebo is unknown given that only saline placebo has been used in prior studies.

Methods: In this trial, 40 patients with major depressive disorder were randomized to receive single intravenous doses of either scopolamine hydrobromide (4–6 μg/kg) or glycopyrronium bromide (4 μg/kg) between August 2019 and April 2021 in Auckland, New Zealand. Glycopyrronium was chosen as the active placebo due to its similar antimuscarinic properties to scopolamine but inability to cross the blood-brain barrier. The primary mood outcome measure was the Montgomery-Åsberg Depression Rating Scale (MADRS) administered pre-infusion and 1, 3, 7, 14, 28, and 42 days post-infusion.

Results: Per protocol, this trial was abandoned for futility at n = 40. While scopolamine reduced MADRS scores by 12.6 (± 8.7 SD) points at day 3, glycopyrronium showed similar reductions (11.2 ± 9.6 SD). Frequentist linear mixed models showed no antidepressant effects of scopolamine versus placebo ($d = 0.17$), and Bayesian mixed effect models showed moderate evidence in favor of the null hypothesis at day 3 (Bayes factor = 0.32). Participants remained well-blinded to drug allocation, with 50% of participants correctly guessing their allocation.

Conclusions: The observed MADRS improvement was larger than in prior studies, but no antidepressant effects were observed. This study using an active placebo confirms recent studies demonstrating the lack of antidepressant efficacy of scopolamine.

Trial Registration: Australian New Zealand Clinical Trials Registry identifier: ACTRN12619000569101

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Major depressive disorder (MDD) is the leading cause of disability, with over 264 million people affected globally.[1] Standard pharmacotherapies have a slow onset of response (typically several weeks) and may have undesirable adverse effects that jeopardize adherence to treatment and quality of life.[2] There is, therefore, a need to identify novel treatments for depression with a faster onset of efficacy. In this regard, ketamine has shown the greatest promise, with numerous clinical trials and meta-analyses[3–5] showing antidepressant effects of intravenous ketamine and a nasal spray enantiomer (esketamine) now an approved medication for treatment-resistant depression.[6]

There is considerable interest in identifying other agents that might show comparable rapid-acting antidepressant effects to ketamine.[7] One such candidate is the antimuscarinic agent scopolamine delivered intravenously at 4 μg/kg, which has been shown in several studies to display antidepressant effects in individuals with MDD.[8–11] However, a recent study failed to replicate scopolamine's antidepressant response.[12] All previous intravenous scopolamine studies utilized the same experimental design with a single-blind saline placebo lead-in followed by a 2-block triplicate infusion paradigm in which scopolamine/saline was administered thrice every 3–5 days and then crossed over to 3 further saline/scopolamine administrations every 3–5 days.

At present, several questions remain regarding scopolamine's antidepressant effect. First, the initial study tested 2–4 μg/kg and found 4 μg/kg to be the most efficacious dose,[8] and subsequent studies continued using this dose.[9–12] It was never established whether or not higher doses of scopolamine yield larger antidepressant effects. Second, the authors used the same triplicate infusion paradigm in all studies, in which 3 scopolamine infusions are administered 3–5 days apart. This triplicate infusion paradigm for scopolamine has not been established as necessary for scopolamine's antidepressant effect. For example, in prior studies, an antidepressant effect is already observed by 3–5 days, at the time of the second dose, so it could be that a single infusion of scopolamine may already elicit an antidepressant response. Third, the purported onset and offset of scopolamine's antidepressant response have not

Clinical Points

- Scopolamine, the next-most-studied rapid-acting antidepressant after ketamine, does not appear to improve depressive symptoms more than placebo.
- Active placebos in clinical trials (such as glycopyrrolate in comparison to scopolamine) can still yield large mood improvements.

been characterized—particularly as past studies reported anecdotal improvements already by 1 day post-infusion.[9] Additionally, the carryover of the antidepressant response is present in the crossover design in past studies with no significant washout period between conditions.[8–10] Lastly, all prior research was conducted using saline placebo without reporting of how much the deblinding, expectancy, and adverse effects of the saline placebo contributed to the placebo response.

To address these issues, we conducted a parallel-group randomized controlled trial of a single dose of scopolamine (4–6 μg/kg) compared to an active placebo glycopyrrolate (4 μg/kg). Like scopolamine, glycopyrrolate is a muscarinic receptor antagonist, but due to its quaternary ammonium compound structure,[13] it cannot cross the blood-brain barrier and, therefore, is a reasonable control mimicking the adverse effect profile and peripheral pharmacologic effects of scopolamine.

METHODS

This trial was prospectively registered in the Australian New Zealand Clinical Trials Registry (registration ACTRN12619000569101). Ethical approval was granted by the Health and Disability Ethics Committee (reference number 18/NTA/206), and the clinical trial protocol was peer-reviewed and prospectively published.[14] Data collection occurred between August 2019 and April 2021 in Auckland, New Zealand.

Participants—Details and Demographics

Forty participants were recruited via self-referral after responding to advertisements on social media and physical posters. Eligibility was assessed by psychiatric trial staff at a screening interview. Participants were in good physical health, were aged 18–60 years, were either male or female, had MDD according to the *DSM-5*,[15] had a MADRS[16,17] score of at least 20, and were medication free for at least 2 weeks (see Supplementary Appendix 1 for more details regarding medication washout). The full inclusion and exclusion criteria are outlined in Supplementary Table 1, and the details and demographics of the participants are summarized in Table 1 (and extensively summarized in Supplementary Table 2). The CONSORT diagram is provided in Supplementary Figure 1. Participants' expectancy was measured using the Credibility Expectancy Questionnaire.[18]

Table 1. Demographic Details of Participants

Demographics	Glycopyrronium (n = 16)	Scopolamine (n = 24)
Age, mean ± SD, y	37.8 ± 11.1	33.0 ± 10.7
Male, n (%)	3 (19)	9 (38)
Ethnicity, n (%)		
European	10 (63)	14 (58)
Māori	1 (6)	4 (17)
Pacific peoples	1 (6)	2 (8)
Asian	2 (13)	3 (13)
MELAA	2 (13)	1 (4)
Weight, mean ± SD, kg	78.6 ± 15.1	82.6 ± 23.6
AUDIT score, mean ± SD	4.8 ± 3.5	3.9 ± 3.4
Previous antidepressants tried, mean ± SD	0.9 ± 0.9	1.4 ± 1.3
CEQ score, mean ± SD	11.38 ± 2.9	11.06 ± 3.9
MADRS score at screening, mean ± SD	27.7 ± 4.4	28.3 ± 4.3
Comorbidities, mean ± SD	2.0 ± 1.5	1.6 ± 1.5
Anxiety disorders, n (%)	14 (88)	17 (71)
Hypomania, n (%)	0 (0)	1 (4)
Substance use disorder (lifetime), n (%)	1 (6)	2 (8)
Any eating disorder, n (%)	0 (0)	0 (0)

Abbreviations: AUDIT = Alcohol Use Disorders Identification Test, CEQ = Credibility Expectancy Questionnaire, MELAA = Middle Eastern/Latin American/African.

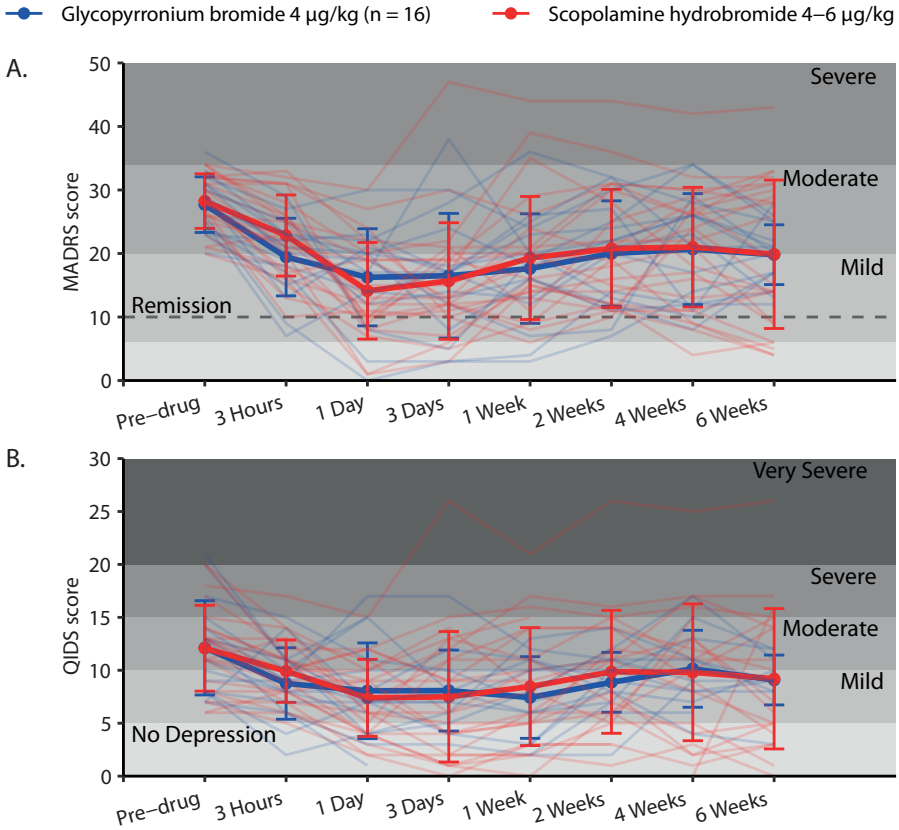
Trial Design

After the screening visit, participants were randomized to receive a single intravenous infusion of either glycopyrronium bromide at 4 μg/kg or scopolamine hydrobromide at 4, 5, or 6 μg/kg in a 2:1:1:1 ratio. On the study day, participants arrived at the research center having already fasted for 2 hours and were set up with 2 intravenous cannulas. Participants received a 15-minute infusion of their assigned drug and concentration using an Alaris PK Syringe Pump (CareFusion, United Kingdom). Participants stayed onsite for 4 hours for monitoring in addition to completing resting-state eyes-open electroencephalography tasks and questionnaires and providing blood samples. These data will be reported in future publications. Participants were followed up at 1, 3, 7, 14, 28, and 42 days post-infusion. The conduct of the trial staff is described further in Supplementary Appendix 2.

Outcomes and Questionnaires

Blinded trial staff completed the MADRS[16,17] on the study day before the drug, at 3 hours post-infusion, and at each of the scheduled follow-up telephone appointments. Blinded trial staff were never present at the interventions or in the immediate follow-up care, to avoid deblinding. The potential therapeutic study staff-participant relationship and MADRS reliability are discussed further in Supplementary Appendixes 3 and 4. The Quick Inventory of Depressive Symptomatology—Self Report (QIDS)[19] was also completed by participants at the same time intervals as the MADRS. The Biphasic Alcohol Effect Scale (BAES),[20] Subjective High Assessment Scale (SHAS),[21] and Clinician-Administered Dissociative States Scale (CADSS)[22] were completed between 35 and 60 minutes post-infusion. The 11-Dimensional Altered State of Consciousness (11DASC) questionnaire[23] was completed at 180 minutes post-infusion. The General

Figure 1. Comparison of Changes Over Time in (A) MADRS Score and (B) Self-Reported QIDS Score in Response to Infusion of Glycopyrronium Bromide Versus Scopolamine Hydrobromide (Aggregated Across 4, 5, and 6 µg/kg)[a]



[a]Points denote mean, error bars denote standard deviation, and faint lines denote individual mood changes.
Abbreviations: MADRS = Montgomery-Åsberg Depression Rating Scale, QIDS = Quick Inventory of Depressive Symptomatology.

Assessment of Side Effects (GASE)[24] was completed at 180 minutes and at 7 days after the study day. The Bowdle visual acuity scale (VAS)[25] was completed before the infusion and at 5, 10, 15, 20, 30, 60, 120, and 240 minutes post-infusion. Vital sign monitoring consisted of hourly blood pressure measurements. The timeline of outcomes and questionnaires is summarized in Supplementary Figure 2 as a SPIRIT figure.

Power Calculations and Stopping Rules

As agreed with the regulator, MedSafe New Zealand, the following power calculations and stopping rules were implemented prior to commencement.[14] Using G*Power 3.1,[26] the primary outcome analysis was the MADRS score at 3 days (as this was most comparable to previous literature) with $\alpha = .05$ and $1 - \beta = 0.80$ between the 3 scopolamine dose groups combined against the active placebo glycopyrronium group. The sample size ratios were 1:1:1:2 to avoid overweighting the treatment group; however, for mood effects analysis, all scopolamine dose groups were combined and compared to the glycopyrronium group. Prospectively published stopping rules stated that interim analysis at n = 40 would declare a negative result, increase the sample size by n = 20, or declare a positive result if the between-drug $d_{interim}$ was < 0.75, 0.75–0.92, or > 0.92, respectively. For an interim analysis in which the conditional power is > 50%, the effect can be considered "promising" and sample size can be increased without biasing the final outcome analysis.[27,28] Had a further 20 participants been recruited, the minimum detectable d_{final} would be 0.75.

Clinical Mood Effects Analysis

The primary outcome measure was the MADRS score analyzed under an intention-to-treat framework using linear mixed models with the package "lme4" using R v4.0.3.[29] For the linear mixed models, drug (scopolamine or glycopyrronium) and time (categorical) were considered as fixed effects and participants as a random (intercept-only) effect. The primary estimand of interest given the literature was the regression coefficient and effect size of the day 3 MADRS measure, as this was the most comparable point to prior literature. Bayesian mixed effect analyses were also conducted to gain posterior densities of the regression coefficients. *R* scripts and data for these analyses are provided here: https://doi.org/10.17608/k6.auckland.19350854. Four minor deviations to protocol are explained in Supplementary Appendix 5.

Table 2. Frequentist and Bayesian Summaries of Mood Scores With the Equation MADRS ~ (Drug × Time) + (1|ID) (Frequentist Analysis Denotes Linear Mixed Model)

	Frequentist			Bayesian				
Parameters	β	*t*	*d*	β	Lower 95% HDI	Upper 95% HDI	Bayes factor	Interpretation of null
Intercept	27.69	13.41	4.33					
Drug	0.56	0.21	0.07	1.00	−3.69	5.63	0.21	Moderate evidence for
Time (3 hour)	−8.25	−4.03	−1.30	−7.26	−10.92	−3.62	135.93	Extreme evidence against
Time (1 day)	−11.44	−5.58	−1.80	−10.50	−14.17	−6.84	11,409.73	Extreme evidence against
Time (3 day)	−11.19	−5.46	−1.76	−10.22	−13.92	−6.58	14,370.54	Extreme evidence against
Time (1 week)	−10.06	−4.91	−1.59	−9.07	−12.68	−5.41	2,701.09	Extreme evidence against
Time (2 weeks)	−7.69	−3.75	−1.21	−6.75	−10.43	−3.09	70.52	Very strong evidence against
Time (4 weeks)	−7.00	−3.42	−1.10	−6.09	−9.73	−2.46	32.35	Very strong evidence against
Time (6 weeks)	−7.88	−3.85	−1.24	−6.96	−10.64	−3.27	97.65	Very strong evidence against
Drug:time (3 hour)	2.83	1.07	0.35	1.92	−2.72	6.57	0.28	Moderate evidence for
Drug:time (1 day)	−2.69	−1.02	−0.33	−3.46	−8.20	1.16	0.63	Anecdotal evidence for
Drug:time (3 day)	−1.40	−0.53	−0.17	−2.22	−6.85	2.39	0.32	Moderate evidence for
Drug:time (1 week)	1.10	0.42	0.13	0.21	−4.52	4.84	0.19	Moderate evidence for
Drug:time (2 weeks)	0.23	0.09	0.03	−0.57	−5.31	4.08	0.19	Moderate evidence for
Drug:time (4 weeks)	−0.25	−0.10	−0.03	−1.05	−5.73	3.60	0.21	Moderate evidence for
Drug:time (6 weeks)	−0.50	−0.19	−0.06	−1.29	−5.99	3.40	0.23	Moderate evidence for

Abbreviations: β = parameter estimate, d = Cohen effect size, HDI = highest density interval, MADRS = Montgomery-Åsberg Depression Rating Scale, *t* = *t* statistic.

Psychotropic Effects, Adverse Effects, Responder Status, and Deblinding

The Bowdle VAS was analyzed as per Zuurman et al,[30] the BAES questionnaire summed 7 sedative and 7 stimulant effect questions, the SHAS and CADSS questionnaires summed all questions' scores, and the 11DASC was analyzed as per Studerus et al.[31] Adverse effects were reported through the GASE questionnaire, but adverse effects were reported only if > 15% of participants in either group reported the effect. The adverse effects of both these medicines are well-described in their product data sheets, so this reporting was used to investigate the extent of blinding.

Participants were recorded as responders if their MADRS score decreased by at least 50%. However, as some participants' mood scores fluctuated between day 1 and day 3, responder status was reported as day-1-only responder, day-3-only responder, or the more liberal day-1-or-3 responder.

Participants were asked at the final 6-week follow-up whether they thought they received scopolamine or the active placebo and asked to rate their confidence in this guess out of 10. Methodological considerations regarding the timing of the guesses are discussed in Supplementary Appendix 6. The percentage of correct guesses and the average confidence ratings were recorded.

RESULTS

The interim analysis at n = 40 yielded a nonsignificant *F* statistic ($F = 0.045$, $P = .83$). The between-drug effect sizes at days 1 and 3 were 0.33 and 0.17, respectively. Following our stopping rules, the trial was abandoned for futility and completed at n = 40, with no significant difference between the mood responses to scopolamine and the active placebo, glycopyrronium.

Table 3. Reported Adverse Effects and De-Blinding Parameters[a]

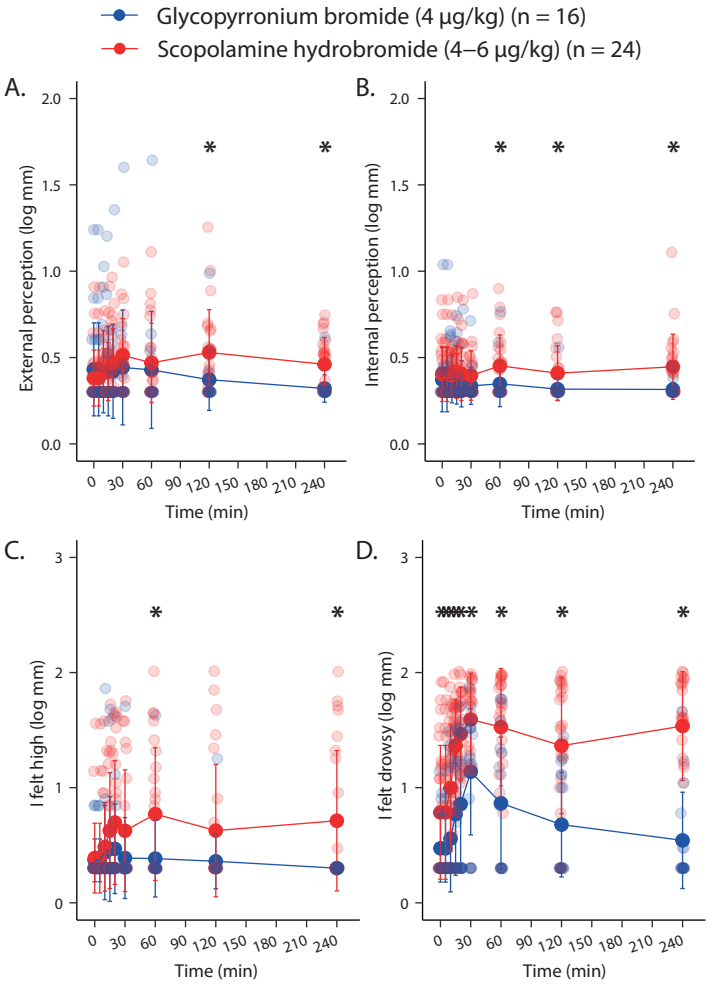
	Glycopyrronium (n = 16)	Scopolamine (n = 24)	Odds ratio (confidence interval)
Adverse effect			
Agitation	0 (0)	5 (21)	7.4 (0.4–143.2)
Dizziness	3 (19)	10 (42)	2.2 (0.5–9.4)
Dry mouth	11 (69)	14 (58)	0.8 (0.3–2.3)
Insomnia	0 (0)	4 (17)	6.1 (0.3–120.3)
Fatigue	2 (13)	7 (29)	2.3 (0.4–12.7)
Palpitations	3 (19)	1 (4)	0.2 (0.02–2.3)
De-blinding			
Participants correct guess	8 (50)	11 (50[b])	1.0 (0.3–3.1)
Participants confidence rating, mean ± SD	5.47 ± 2.58	5.70 ± 2.67	
Rater correct guess	6 (38)	17 (77[b])	2.1 (0.7–6.4)
Rater confidence rating, mean ± SD	5.33 ± 2.32	6.01 ± 2.44	
Responders			
At day 1	4 (25)	13 (54)	2.2 (0.6–7.8)
At day 3	6 (38)	12 (50)	1.3 (0.4–4.3)
At either day 1 or day 3	6 (38)	16 (67)	1.8 (0.6–5.5)

[a]Values expressed as count of events (%) unless otherwise noted.
[b]The denominator for these calculations was 22 due to 2 protocol deviations.

Mood Responses to Scopolamine and Placebo

Following scopolamine and glycopyrronium infusions, there were large reductions in MADRS scores. Glycopyrronium and scopolamine improved mood scores (± SD) by 11.4 ± 8.2 and 14.1 ± 7.3 MADRS points at day 1, respectively, and 11.2 ± 9.6 and 12.6 ± 8.7 MADRS points at day 3, respectively (Figure 1A, Table 2). The corresponding effect sizes at day 3 for glycopyrronium and scopolamine were 1.93 and 2.17, respectively. However, the between-drug effect size favoring scopolamine was 0.17. On average, participants entered the trial with moderate depression, and their mood improved on average to mild depression by 3 days (Figure 1A). The self-reported QIDS also showed consistent results

Figure 2. Psychotropic and Basic Physiologic Effects of Glycopyrronium and Scopolamine[a]



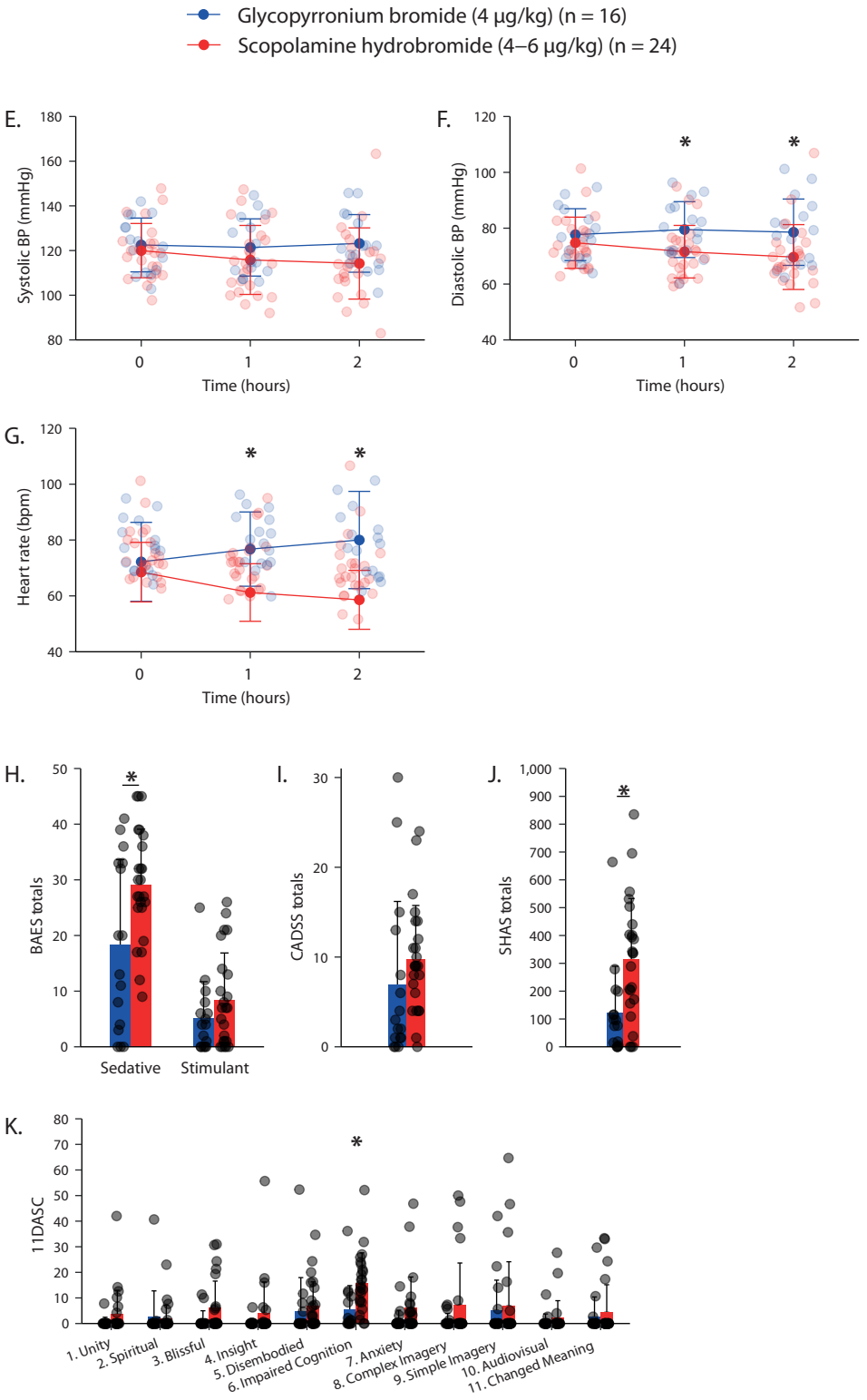
[a]Points and bars denote mean, error bars denote standard deviation, and faded points denote individual data.
*Statistically significant by unprotected Welch *t* test (α = .05).
Abbreviations: 11DASC = 11-Dimensional Altered States of Consciousness, BAES = Biphasic Alcohol Effects Scale, CADSS = Clinician-Administered Dissociative States Scale, SHAS = Subjective High Assessment Scale.

with the average participant's depressive symptoms changing from moderate (12.1 ± 4.5 and 12.1 ± 4.1) to mild (8.1 ± 3.8 and 7.5 ± 6.2) at 3 days post-infusion (for glycopyrronium and scopolamine, respectively) (Figure 1B). Despite these large magnitude mood improvements, no significant effect was found between glycopyrronium and scopolamine. In frequentist linear mixed model analyses, the 3-day between-drug effect size favoring scopolamine was 0.17, which yielded a lack of evidence against the null hypothesis (Table 2). The residuals for this linear mixed model appeared normally distributed (Shapiro *P* value = .282). The Bayesian analysis at 3 days yielded a Bayes factor of 0.32, indicating moderate evidence for the null hypothesis (Table 2). The scopolamine group had a higher but nonsignificant day 1 or 3 responder rate than glycopyrronium (odds ratio [95% CI] = 1.8 [0.6–5.5], *P* = .32, Table 3). Regarding the potential covariates dose, sex, MADRS baseline severity, and number of medications tried, significant confounding effects were not observed, but this was attributed to lack of power (see Supplementary Appendix 7).

Psychotropic, Adverse, and Deblinding Effects

Overall, the psychotropic and adverse effect profile of the 2 drugs appeared to be roughly similar, with the most reported adverse effect being dry mouth. No treatment-emergent serious adverse events were detected. The Bowdle VAS showed slight increases in external and internal perception acutely in both groups, but the glycopyrronium group appeared to abate more quickly on average. In contrast, the scopolamine group appeared to persist with changes to external and internal perception leading to significant differences particularly at 120 and 240 minutes between the 2 groups (Figure 2A and 2B). Glycopyrronium caused some feelings of a "high" acutely (Figure 2C), but

Figure 2 cont'd. Psychotropic and Basic Physiologic Effects of Glycopyrronium and Scopolamine[a]



[a]Points and bars denote mean, error bars denote standard deviation, and faded points denote individual data.
*Statistically significant by unprotected Welch *t* test (α = .05).
Abbreviations: 11DASC = 11-Dimensional Altered States of Consciousness, BAES = Biphasic Alcohol Effects Scale, CADSS = Clinician-Administered Dissociative States Scale, SHAS = Subjective High Assessment Scale.

scopolamine caused greater feelings of a "high" as shown in the SHAS (Figure 2J) and for longer, leading to significant differences in the VAS at 60 and 240 minutes (Figure 2C). Comparatively, while both glycopyrronium and scopolamine caused feelings of drowsiness, scopolamine caused greater sedative effects according to the BAES (Figure 2H) and at every time point recorded in the VAS (Figure 2D). Comparatively, no dissociative effects were recorded by the CADSS (Figure 2I, 2K), though scopolamine caused feelings of "slow"-ness, which contributed to the difference in impaired cognition in the 11DASC (Figure 2K). Systolic blood pressure did not change significantly, but scopolamine lowered diastolic blood pressure and heart rate. In contrast, glycopyrronium caused increased diastolic blood pressure and heart rate, leading to significant differences at 1 and 2 hours post-infusion (Figure 2F, 2G). The effects of the drugs usually subsided by the end of the day.

Participants were well blinded to the drug they were receiving, with only 50% of participants in both groups guessing the drug they received correctly with similar confidence ratings (Table 3). The MADRS rater appeared to more frequently guess scopolamine (77%) correctly than glycopyrronium (38%), but with similar confidence ratings across both groups.

DISCUSSION

Evaluation of Antidepressant Effects of Scopolamine

The present trial indicates that scopolamine has no antidepressant effect in patients with MDD. This is due to the lack of difference in the antidepressant responses between scopolamine and glycopyrronium (Table 2, Figure 1A). Moreover, Bayesian analysis provides moderate evidence in favor of the null hypothesis of no between-drug effect. Notably, both treatment and control groups retained similar levels of blinding near chance and similar pre-trial expectancy (Table 1). The simplest explanation of the mood improvements observed in both groups is due to placebo responses.

However, the baseline to day 3 MADRS improvements of 12.6 observed for scopolamine are larger than previous findings. From the 5 published IV scopolamine studies, average baseline to day 3 post-scopolamine infusion changes ranged from 4.1–9.6 MADRS improvements when scopolamine was administered first, or 2.6–12.5 MADRS improvements when scopolamine was administered after the crossover.[8–12] The differences in mood improvements may be accounted for by study design and differing placebo. Prior studies utilize single-blind lead-in designs which may diminish the placebo response,[32] but may also lead to increased drug-placebo treatment differences in antidepressant studies.[33] Lastly, given that treatment resistance is negatively associated with placebo response magnitude,[34–36] our relatively treatment-naïve cohort exhibiting larger mood improvements is congruent with the results found by Park et al,[12] whose recent negative trial of scopolamine was attributed to a more severely depressed and treatment-resistant cohort. Overall, differing study designs may explain why the MADRS improvements in the present study are larger and more similar between the drug and active placebo groups.

The use of saline placebo may cause deblinding effects, which may, in turn, diminish the placebo effect. The previous crossover studies mentioned that blinding was harder to maintain, particularly in the scopolamine/placebo group.[9] These participants would have already experienced the active drug scopolamine, so receiving the saline placebo in the second arm may cause said deblinding effects, which diminish the placebo effect. Furthermore, alongside deblinding effects, saline may also cause a "disappointment" effect, which also diminishes the placebo effect. This has been observed in 2-arm clinical trials for ketamine, where MADRS improvements of 7.0 are observed for midazolam (active) placebos and 1.6 for saline placebos.[37] As a result of the differing study design and the use of saline placebos, the combination of inadequate blinding and the greater "disappointment" effect in the saline placebo arm has potentially exposed past research to false positives.

An alternative interpretation is that glycopyrronium may be acting as an antidepressant by peripheral antimuscarinic effects. Given that peripheral antimuscarinic effects have already been suggested to be a mechanism of action for scopolamine's antidepressant effect,[9] this could implicate the peripheral antimuscarinic effects and, subsequently, the parasympathetic nervous system in depressive etiology. A potential mechanism of action could be that depressed individuals have higher rates of stress and, therefore, an underactive or atypical parasympathetic nervous system (PSNS).[38] Acutely blocking the PSNS via antimuscarinic agents could reset or restore regular PSNS activity. Previous research has shown that scopolamine increased heart rate variability and PSNS activity in healthy individuals and patients with heart failure 24 hours post-administration.[39–41] However, glycopyrronium (and a variety of other anticholinergic drugs) have been used for over 50 years in various domains of medicine[13] with no reports of antidepressant effects. Furthermore, to have stumbled across the optimal dose and therapeutic time window in this trial by coincidence would be unlikely. Moreover, the muscarinic receptor binding profiles of scopolamine and glycopyrrolate are different,[42,43] and preclinical models of scopolamine's potential mechanism of action in depression are centered around central nervous system activity.[7,44–46] Taken together, while we cannot exclude this possibility, it is an improbable scenario. Comparatively, the similar expectancy, adverse effect profile of both drugs, and strong blinding make it more likely that the large antidepressant responses observed are due to large placebo responses. This finding highlights the importance of adequate blinding because successful blinding (such as in this study) can nullify large antidepressant effects.

Psychotropic, Adverse, and Deblinding Effects and Responder Status

Scopolamine had a more prolonged and intense psychotropic, sedative, antisialic, and adverse effect profile (Figure 2, Table 3). Comparatively, participants in the glycopyrrolate only showed mild central nervous system effects like drowsiness—though this was possibly due to being seated for extended periods of time. As participants received only 1 drug (ie, participants had no comparison to make as in crossover), it was difficult for participants to guess the correct drug leading to the 50% correct guess rate. Particularly as participants were only given the opportunity to guess at the end of 6 weeks, there may also have been recollection biases. Raters have access to participants' mood changes over the 6 weeks, therefore, achieving 38% and 77% correct guess rates for glycopyrronium and scopolamine, respectively, matches with the 38% and 67% responder rates for glycopyrronium and scopolamine, respectively. By choosing an active placebo with a very similar adverse effect profile, along with utilizing a single-phase study where participants only receive 1 of the drugs, better blinding was achieved for both participants and raters than previous studies with scopolamine.

Strengths and Limitations

The high adherence to protocol, pre-publication of power calculations, predefined stopping rules, disclosure of deblinding effects, and participant expectancy effects were all strengths of the study. The use of an active placebo, glycopyrronium was also a strength that appeared to provide strong blinding effects and equalized the placebo effect in both groups.

However, the use of only an active placebo, glycopyrronium, is also a limitation. As past studies utilized saline placebos, this makes a comparison with past research nonequivalent. Other active placebos such as midazolam[47,48] and remifentanil[49] have been used in assessing ketamine's antidepressant effect. Future research in scopolamine using said active placebo comparators may provide better comparability to previous research with ketamine and active placebos.

CONCLUSION

This study presents evidence to suggest that scopolamine is not an antidepressant, as the mood changes after scopolamine infusion are not larger than after active placebo infusion. While this study yields larger depressive mood improvements than in prior studies, a well-controlled trial can cause even a large antidepressant effect to disappear.[50] Therefore, this trial calls into question the appropriate choice of an active placebo and emphasizes the importance of strong blinding conditions to control expectancy effects in clinical trials of mood disorders.

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REFERENCES

1. World Health Organization. Depression. https://www.who.int/news-room/fact-sheets/detail/depression. Published January 30, 2020. Accessed July 4, 2021.
2. Kelly K, Posternak M, Alpert JE. Toward achieving optimal response: understanding and managing antidepressant side effects. *Dialogues Clin Neurosci*. 2008;10(4):409–418.
3. Lee EE, Della Selva MP, Liu A, et al. Ketamine as a novel treatment for major depressive disorder and bipolar depression: a systematic review and quantitative meta-analysis. *Gen Hosp Psychiatry*. 2015;37(2):178–184.
4. Fond G, Loundou A, Rabu C, et al. Ketamine administration in depressive disorders: a systematic review and meta-analysis. *Psychopharmacology (Berl)*. 2014;231(18):3663–3676.
5. Marcantoni WS, Akoumba BS, Wassef M, et al. A systematic review and meta-analysis of the efficacy of intravenous ketamine infusion for treatment resistant depression: January 2009–January 2019. *J Affect Disord*. 2020;277:831–841.
6. Canady VA. FDA approves esketamine treatment for MDD, suicidal ideation. *Ment Health Wkly*. 2020;30(31):6–7.
7. Duman RS. Ketamine and rapid-acting antidepressants: a new era in the battle against depression and suicide. *F1000 Res*. 2018;7:659.
8. Furey ML, Drevets WC. Antidepressant efficacy of the antimuscarinic drug scopolamine: a randomized, placebo-controlled clinical trial. *Arch Gen Psychiatry*. 2006;63(10):1121–1129.
9. 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):432–438.
10. Furey ML, Khanna A, Hoffman EM, et al. Scopolamine produces larger antidepressant and antianxiety effects in women than in men. *Neuropsychopharmacology*. 2010;35(12):2479–2488.
11. Ellis JS, Zarate CA Jr, Luckenbaugh DA, et al. Antidepressant treatment history as a predictor of response to scopolamine: clinical implications. *J Affect Disord*. 2014;162:39–42.
12. Park L, Furey M, Nugent AC, et al. Neurophysiological changes associated with antidepressant response to ketamine not observed in a negative trial of scopolamine in major depressive disorder. *Int J Neuropsychopharmacol*. 2019;22(1):10–18.
13. Mirakhur RK, Dundee JW. Glycopyrrolate: pharmacology and clinical use. *Anaesthesia*. 1983;38(12):1195–1204.
14. Chen JCC, Sumner RL, Krishnamurthy Naga V, et al. A randomised, double-blind, active placebo-controlled, parallel groups, dose-response study of scopolamine hydrobromide (4-6 µg/kg) in patients with major depressive disorder. *Trials*. 2020;21(1):157.
15. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. American Psychiatric Publishing; 2013.
16. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
17. Williams JB, Kobak KA. Development and reliability of a structured interview guide for the Montgomery Asberg Depression Rating Scale (SIGMA). *Br J Psychiatry*. 2008;192(1):52–58.
18. Rutherford BR, Marcus SM, Wang P, et al. A randomized, prospective pilot study of patient expectancy and antidepressant outcome. *Psychol Med*. 2013;43(5):975–982.
19. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003;54(5):573–583.
20. Martin CS, Earleywine M, Musty RE, et al. Development and validation of the Biphasic Alcohol Effects Scale. *Alcohol Clin Exp Res*. 1993;17(1):140–146.
21. Judd LL, Hubbard RB, Huey LY, et al. Lithium

carbonate and ethanol induced "highs" in normal subjects. *Arch Gen Psychiatry*. 1977;34(4):463–467.
22. Bremner JD, Krystal JH, Putnam FW, et al. Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). *J Trauma Stress*. 1998;11(1):125–136.
23. Dittrich A. The standardized psychometric assessment of altered states of consciousness (ASCs) in humans. *Pharmacopsychiatry*. 1998;31(suppl 2):80–84.
24. Rief W, Barsky AJ, Glombiewski JA, et al. Assessing general side effects in clinical trials: reference data from the general population. *Pharmacoepidemiol Drug Saf*. 2011;20(4):405–415.
25. Bowdle TA, Radant AD, Cowley DS, et al. Psychedelic effects of ketamine in healthy volunteers: relationship to steady-state plasma concentrations. *Anesthesiology*. 1998;88(1):82–88.
26. Faul F, Erdfelder E, Lang AG, et al. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*. 2007;39(2):175–191.
27. Chen YHJ, DeMets DL, Lan KKG. Increasing the sample size when the unblinded interim result is promising. *Stat Med*. 2004;23(7):1023–1038.
28. Chen YH, Li C, Lan KK. Sample size adjustment based on promising interim results and its application in confirmatory clinical trials. *Clin Trials*. 2015;12(6):584–595.
29. R Core Team. *A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing. https://www.r-project.org/. 2020. Accessed June 22, 2021.
30. Zuurman L, Roy C, Schoemaker RC, et al. Effect of intrapulmonary tetrahydrocannabinol administration in humans. *J Psychopharmacol*. 2008;22(7):707–716.
31. Studerus E, Gamma A, Vollenweider FX. Psychometric evaluation of the altered states of consciousness rating scale (OAV). *PLoS One*. 2010;5(8):e12412.
32. Harden RN, Saracoglu M, Connolly S, et al. "Managing" the placebo effect: the single-blind placebo lead-in response in two pain models. *Pain Med*. 2016;17(12):2305–2310.
33. Faries DE, Heiligenstein JH, Tollefson GD, et al. The double-blind variable placebo lead-in period: results from two antidepressant clinical trials. *J Clin Psychopharmacol*. 2001;21(6):561–568.
34. Brown WA, Johnson MF, Chen MG. Clinical features of depressed patients who do and do not improve with placebo. *Psychiatry Res*. 1992;41(3):203–214.
35. Fairchild CJ, Rush AJ, Vasavada N, et al. Which depressions respond to placebo? *Psychiatry Res*. 1986;18(3):217–226.
36. Sullivan MD, Katon WJ, Russo JE, et al. Patient beliefs predict response to paroxetine among primary care patients with dysthymia and minor depression. *J Am Board Fam Pract*. 2003;16(1):22–31.
37. Wilkinson ST, Farmer C, Ballard ED, et al. Impact of midazolam vs saline on effect size estimates in controlled trials of ketamine as a rapid-acting antidepressant. *Neuropsychopharmacology*. 2019;44(7):1233–1238.
38. Yaroslavsky I, Rottenberg J, Bylsma LM, et al. Parasympathetic nervous system activity predicts mood repair use and its effectiveness among adolescents with and without histories of major depression. *J Abnorm Psychol*. 2016;125(3):323–336.
39. De Ferrari GM, Mantica M, Vanoli E, et al. Scopolamine increases vagal tone and vagal reflexes in patients after myocardial infarction. *J Am Coll Cardiol*. 1993;22(5):1327–1334.
40. La Rovere MT, Mortara A, Pantaleo P, et al. Scopolamine improves autonomic balance in advanced congestive heart failure. *Circulation*. 1994;90(2):838–843.
41. Vybiral T, Bryg RJ, Maddens ME, et al. Effects of transdermal scopolamine on heart rate variability in normal subjects. *Am J Cardiol*. 1990;65(9):604–608.
42. Haddad EB, Patel H, Keeling JE, et al. Pharmacological characterization of the muscarinic receptor antagonist, glycopyrrolate, in human and guinea-pig airways. *Br J Pharmacol*. 1999;127(2):413–420.
43. Bolden C, Cusack B, Richelson E. Antagonism by antimuscarinic and neuroleptic compounds at the five cloned human muscarinic cholinergic receptors expressed in Chinese hamster ovary cells. *J Pharmacol Exp Ther*. 1992;260(2):576–580.
44. Drevets WC, Zarate CA Jr, Furey ML. Antidepressant effects of the muscarinic cholinergic receptor antagonist scopolamine: a review. *Biol Psychiatry*. 2013;73(12):1156–1163.
45. Duman RS. Neurobiology of stress, depression, and rapid acting antidepressants: remodeling synaptic connections. *Depress Anxiety*. 2014;31(4):291–296.
46. Ghosal S, Bang E, Yue W, et al. Activity-dependent brain-derived neurotrophic factor release is required for the rapid antidepressant actions of scopolamine. *Biol Psychiatry*. 2018;83(1):29–37.
47. Dwyer JB, Landeros-Weisenberger A, Johnson JA, et al. Efficacy of intravenous ketamine in adolescent treatment-resistant depression: a randomized midazolam-controlled trial. *Am J Psychiatry*. 2021;178(4):352–362.
48. Shiroma PR, Thuras P, Wels J, et al. A randomized, double-blind, active placebo-controlled study of efficacy, safety, and durability of repeated vs single subanesthetic ketamine for treatment-resistant depression. *Transl Psychiatry*. 2020;10(1):206.
49. McMillan R, Sumner R, Forsyth A, et al. Simultaneous EEG/fMRI recorded during ketamine infusion in patients with major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2020;99:109838.
50. Muthukumaraswamy SD, Forsyth A, Lumley T. Blinding and expectancy confounds in psychedelic randomized controlled trials. *Expert Rev Clin Pharmacol*. 2021;14(9):1133–1152.

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