The effects of intramuscular administration of scopolamine augmentation in moderate to severe major depressive disorder: a randomized, double-blind, placebo-controlled trial

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Abstract

Introduction: Major depressive disorder (MDD) is a common affective disorder. Currently established pharmacotherapies lack rapid clinical response, thereby limiting their ability to bring instant relief to patients. A series of clinical trials has demonstrated the antidepressant effects of scopolamine, yet few have studied the effects of add-on scopolamine to currently available antidepressants. It is not known whether conventional antidepressant treatment with a 3-day scopolamine injection could speed up oral antidepressant efficacy. The main focus of this study is to detect the capacity of the rapid-onset efficacy of such a treatment option.

Methods and analysis: This study consisted of a single-centre, double-blind, three-arm randomized trial with a 4-week follow-up period. Sixty-six participants meeting entry criteria were randomly allocated to three treatment groups: a high-dose group, a low-dose group and a placebo control group. Psychiatric rating scales were administered at baseline and seven viewing points following the administration of intramuscular injections. The primary outcome measure was length of time from randomization (baseline) to early improvement.

Results: Both primary and secondary outcome measures consistently showed no differences among the three groups. The cumulative response rate and the remission rate were 72.7% (48/66) and 47.0% (31/66). Intramuscular scopolamine treatment was relatively well tolerated. Two subjects with high-dose injections dropped out because of a drug-related side effect.

Conclusion: Contrary to our prediction, we found that, compared to placebo (0.9% saline i.m.), scopolamine was not associated with a significantly faster antidepressant response rate.

Trial registration: ClinicalTrials.gov, NCT03131050. Registered on 18 April 2017.

Keywords: add-on, efficacy, intramuscular, major depressive disorder, scopolamine

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Background

Major depressive disorder (MDD) is a common neuropsychiatric illness that may affect up to 17% of the population and is associated with significant social and economic burdens.[1–4] In China, MDD has been found to be the most prevalent mood disorder (life-time prevalence 3.4% and 12-month prevalence 2.1%).[5] Current pharmacotherapies lack rapid clinical response, thereby limiting their ability to bring instant relief to patients.[6] The development of rapid-acting treatments for individuals who fail to respond to conventional antidepressant treatments is an urgent public health need, particularly because of an enhanced risk of suicide and disability in these patients.[7,8]

Psychopharmacological research over the past few decades has not significantly advanced the number of approved drug treatments for depression beyond the monoaminergic interventions in use for over 50 years. The only new drug, an FDA-approved nasal spray for treatment-resistant depression and suicidal ideation, was finally approved on 5 March 2019. Thus, the need to develop novel and rapid antidepressant treatments is great and will likely require the targeting of novel neurobiological substrates. A series of studies have demonstrated the potential benefit of novel approaches such as the N-methyl-D-aspartate antagonist ketamine,[9,10] demonstrating a significant alleviation in symptoms within hours, though only transiently and with symptoms typically resurfacing within days following discontinuation of the acute intervention. Significant clinical improvements in depressive symptomatology have been observed after ketamine administration, but its safety and toxicity profile continue to remain a concern.

Hyperactivity in the muscarinic cholinergic receptor system has been implicated in the pathophysiology of depression. There is growing interest in whether the nonspecific antagonist scopolamine has the potential to be effective as an antidepressant treatment.[11] Scopolamine is an antimuscarinic agent targeting cholinergic muscarinic receptors and primarily used for postoperative nausea, gastrointestinal disorders and motion sickness. In recent years, a series of clinical trials have demonstrated the antidepressant effects of scopolamine. The results showed that patients with depression demonstrated a rapid and consistent decline in Montgomery–Asberg Depression Rating Scale (MADRS) scores 3 days after the first infusion.[12–15] Animal studies have demonstrated that scopolamine can block muscarinic receptors on γ-aminobutyric acid (GABA)ergic interneurons and decreases GABA inhibition, resulting in excitation of pyramidal cells, enhanced glutamate release and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) activation, which then leads to the activation of the mammalian target of rapamycin complex 1 (mTORC1) signalling pathway and rapidly increased synaptogenesis in a rapamycin-sensitive manner in the rat prefrontal cortex.[16,17]

Previous studies only addressed the effects of intravenous (i.v.) scopolamine (4 μg/kg), which may be difficult to use in a clinical setting, particularly the outpatient one. This study uses intramuscular (i.m.) injections. Compared with an i.v. scopolamine infusion, the use of i.m. injections in patients is more convenient and also generally more acceptable. More importantly, in China the indications for scopolamine injection are i.m. and subcutaneous administrations only, but not i.v. infusions. Although i.m. injections of scopolamine were shown to have small and transient antidepressant effect in one of the previous studies, there were limitations associated with that particular investigation, including the small number of cases and gender bias.[18] Thus, an improved study design would be better able to further explore the efficacy of i.m. injections.

The effect of add-on scopolamine to currently available antidepressants has not been examined. It is not known whether conventional antidepressant treatment with a 3-day scopolamine injection could speed up oral antidepressant efficacy. Due to the lack of a known effective dose of i.m. scopolamine from previous studies, we designed a dose-finding study employing a scopolamine dose range that was previously associated with cognitive effects but not toxic ones. The instructions specify a single dose of scopolamine of 0.3–0.5 mg and a daily dose of 1.5 mg. We aimed to determine the antidepressant effects of low-dose (0.3 mg/day) and high-dose (0.6 mg/day, an i.m. injection of 0.3 mg was given at 6-hour intervals) i.m. scopolamine combined with escitalopram initiation in MDD patients. To detect the rapid-onset capacity of the treatment was the main goal of this study.

We hypothesized that compared to placebo (0.9% saline i.m.), scopolamine augmentation of escitalopram would be associated with a significantly faster antidepressant response. The primary outcome measure was the time from randomization (baseline) to early improvement [at least 20% reduction on the 17-Item Hamilton Depression Rating Scale (HRSD17)].[19] Secondary outcome measures were response rates (at least 50% decrease on the HRSD17 at any visit from baseline), remission rates (HRSD17 total scores ≤7) at day 28, changes in HRSD17 total scores, Quick Inventory of Depressive Symptomatology Self Report 16-Item (QIDS-SR16) scores, Generalized Anxiety Disorder 7-Item (GAD-7) scores and Young Mania Rating Scale (YMRS) scores from baseline to any visit, changes in the Clinical Global Impression of Severity (CGI-S) scores from baseline to the end of the trial, and the Clinical Global Impression of Improvement (CGI-I) scores at any visit.

Methods

Patients and study settings

The study consisted of a single-centre, double-blind, three-arm randomized trial with a 4-week follow-up period at Beijing Anding Hospital, Capital Medical University. The protocol is described in more detail by Zhou et al.[20] [ClinicalTrials.gov Identifier: NCT03131050].

All patients were diagnosed in outpatient clinics from 15 March 2017 to 8 February 2018. Inclusion criteria included age between 18 years and 45 years, a diagnosis of MDD using the Structured Clinical Interview for DSM-IV criteria, and a HRSD17 total score ≥20. Exclusion criteria included a history of any clinically significant disease or clinically significant laboratory abnormalities that are not stabilized or anticipated to require treatment during the study, a positive pregnancy test or breast-feeding, antipsychotic or mood stabilizer use within 5 days prior to screening, an allergy to or lack of response to escitalopram, electroconvulsive therapy (ECT) or modified ECT within the months prior to screening, smoking, significant risk of suicidality as per scoring 3 or 4 on HRSD17 Item 3, and risk of self-harm behaviours as assessed by the investigator.

The protocol was approved by the ethical review committee of the Beijing Anding Hospital (No. 2016–106, Beijing, China). There were no changes to the protocol in the course of the study. The study was conducted in accordance with the Declaration of Helsinki. All subjects were free to withdraw at any time during the study. All study participants signed a written informed consent. The patients and nurses administering the injections were blinded to the patients' group assignments. The unblinded pharmacist was accountable for the drug preparation. The investigators assessing outcome and adverse events were blinded to the treatment allocation. Therefore, the blinding was not interrupted.

Study design

Sixty-six subjects meeting entry criteria were equally and randomly allocated to three treatment groups (22 per group) that were different for the first 3 days only. All individuals who received i.m. injections stayed on emergency wards for the first 3 days and received clinical visits on the 4th, 7th, 14th, and 28th day.

High-dose group: subjects received 0.3 mg i.m. scopolamine twice daily (9 am; 3 pm) for 3 days.
Low-dose group: subjects received 0.3 mg i.m. scopolamine once daily (9 am) and saline once daily (3 pm) for 3 days.
Saline control group: subjects received i.m. saline twice daily (9 am; 3 pm) for 3 days.

Participants in all three groups were treated with oral escitalopram with a dose of 10 mg/day administered for the first 3 days of add-on injections as well as for the subsequent 25 days. Selective serotonin-receptor inhibitors (SSRIs) have emerged as the first-line option in treating depression due to their superior safety profile compared to older antidepressants such as tricyclic antidepressants and monoamine oxidase inhibitors.[21] Escitalopram was chosen as it is one of the most commonly prescribed SSRIs in China.

Antipsychotics, mood stabilizers and other antidepressants were prohibited during the study. Use of non-benzodiazepines such as zolpidem (≤10 mg/day), zopiclone (≤7.5 mg/day) and zaleplon (≤10 mg/day) were permitted in patients with severe insomnia. Benzodiazepines such as lorazepam were permitted in patients with significant anxiety symptoms but not for the first 8 h prior to assessment. ECT, transcranial magnetic stimulation, phototherapy, electro-acupuncture, biofeedback, and vagal nerve stimulation were also prohibited. Any systematic psychotherapy (psychoanalysis, cognitive comprehension, desensitization therapy, hypnosis therapy, Morita therapy) was prohibited, but general supportive psychotherapy was acceptable.

Outcomes and assessments

Before each injection, depression severity was rated using the Chinese version of the HRSD17 and MADRS.[22–24] The development of hypomanic symptoms was assessed using the YMRS.[24] The CGI scale[25] was applied as a global assessment of illness severity. The QIDS-SR16[26] and GAD-7[27] were used to evaluate depression severity and anxiety symptoms, respectively. The primary outcome for this study was the time from randomization (baseline) to early improvement (at least 20% reduction in HRSD17 scores). Secondary outcomes included response rates (a 50% decrease in HRSD17 scores from baseline), remission rates (HRSD17 scores ≤7), changes in HRSD17, MADRS, QIDS-SR16, GAD-7, YMRS, and CGI Scale scores throughout the

trial. Udvalg for Kliniske Undersogelser (UKU) was used to assess adverse events at each visit point.[28]

The scales were administered at baseline and day 1 (4 h), day 2, day 3, day 4, day 7, day 14 and day 28 following the initiation of the i.m. injection. Blood pressure and heart rate were measured at each visit. Inter-rater reliability (kappa values for categorical measures) was >0.8 for all measurements.

Sample size
According to published research and clinical expectations,[29] we estimated the median time from baseline to early improvement of scopolamine plus escitalopram as 6.4 days and the 4-week remission rate as 92.3%. The median time from baseline to early improvement of placebo plus escitalopram treatments is 26.5 days and the 4-week remission rate is 57.1%. Considering the time to early improvement, which is fitted to an exponential distribution, and assuming a power of 80% with a two-sided significance of 0.01, a minimal sample size of 54 was calculated using survival (time to event) modules. A common method for testing the proportional hazards assumption is to include a time interaction term to determine whether the hazard ratio changes over time, since time is often the culprit behind non-proportionality of the hazards. Evidence that the group $\times$ time interaction term is not zero is evidence against proportional hazards. Assuming an attrition rate of 10%, at least 66 participants were required.

Statistical analysis
The analysis was conducted based on the intent-to-treat principle. Kaplan-Meier analyses were used to calculate the estimated time from baseline to all-cause response and remission during the 4-weeks visit. The cox proportional hazards regression model was used to compare the estimated time to recurrence between groups while controlling for covariates such as recurrence history and length of current depressive episode at baseline. Baseline socio-demographic and clinical characteristics were compared between groups using independent ANOVA, Mann–Whitney U test, χ^2 tests and Fisher's exact test. Secondary analyses were performed to assess changes from baseline to week 4 on QIDS-SR16 total score and CGI-S score, using mixed model for repeated measures (FAS, MMRM), with treatment as the fixed factor and baseline score covariates. LSMEANS were used to compare differences among groups. Multi-comparison was made under a null hypothesis. Method of step-down was used to control type I error spending. We compared higher dose with placebo, and if any significance existed comparisons would continue. The step-down Bonferroni for p value adjustment was used. Significance was set at 0.05 (two-side) and data was analysed using SAS9.4 software (SAS Institute Inc., Cary, North Carolina, USA).

Results

Patients
Of the 77 potential patients who signed the informed consent form and were screened, 66 met all the study criteria and were randomized using a 1:1:1 ratio. The trial profile is shown in Figure 1. During the 4-week study, a total of 11 subjects withdrew. The proportion of dropouts was distributed equally across the groups ($p = 0.7698$). Of the 11 subjects who withdrew from the study, the mean age was 26.3 (SD = 24.5), 72.7% (8/11) were female and the average total score of HRSD17 was 26.7 (SD = 5.8). None of these characteristics differed statistically between the subjects who withdrew and those who completed all study visits (p value all >0.05).

Demographics and clinical characteristics
Demographics and clinical characteristics for each group are listed in Table 1. The three groups were comparable with regard to age, sex and psych-medical health. Baseline HRSD scores did not differ among the three groups (mean ± SD for placebo, 24.5 ± 5.0; low dose, 25.7 ± 4.7; high dose, 25.4 ± 4.2; $p = 0.6996$).

Treatment features (protocol medications and compliance)
Drug pills were counted to measure compliance with the protocol. Comprehensive compliance was over 80%. A total of 14 patients were prescribed short-acting benzodiazepines to address insomnia and anxiety problems.
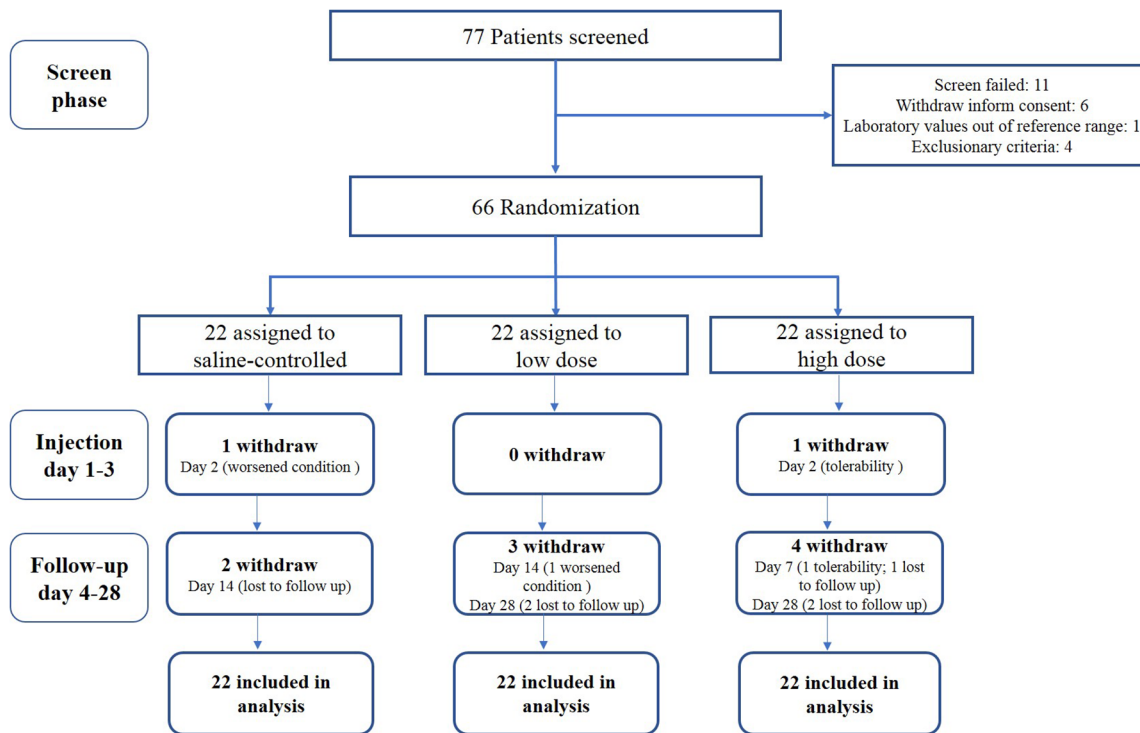
Figure 1. Flow chart of the trial.

Symptom outcomes

Primary outcome. A total of 61 subjects met the criteria for improvement at week 4. The estimated interval for improvement in the three groups in the Kaplan–Meier analysis is illustrated in Figure 2. The average time until designated improvement (at least 20% reduction in HRSD17 scores) was 3 days (95% CI: 2–7) in the high-dose group, 3 days (95% CI: 2–7) in the low-dose group and 3 days (95% CI: 3–4) in the placebo group (Figure 2(a)). The difference in cumulative response rate among the three groups showed no statistical significance ($-2\text{Log (LR)} = 3.1485$, $p = 0.2072$) (Figure 2(b)). The cumulative response rate and the remission rate were 72.7% (48/66) and 47.0% (31/66), respectively (Figure 2(c)).

Secondary outcome. The difference in change of total scores of efficacy measures yielded results consistent with the cumulative rates analysis. There were no significant differences among groups on change from baseline to end visit for the total scores of HRSD17, MARDS, QIDS-SR16, GAD-7 and CGI-S. Regarding the MMRM analysis of the total scores, the CI for the difference between the groups included zero (Table 2).

Tolerability and adverse events

As shown in Table 3, two subjects in the high-dose group dropped out because of a drug-related side effect. Both patients developed a transient disturbance of consciousness during the i.m. injection of scopolamine. Symptoms disappeared within 24 h after stopping the i.m. injection.

Ten adverse events including blurred vision, dizziness, somnolence, nausea, fatigue, drowsiness, dry mouth, anxiety, insomnia, and tachycardia were recorded throughout the study. The proportion of event type and the total number of adverse events differed significantly among the three groups ($p = 0.0024$).

There were no significant differences in the side effects–UKU global assessment among the three groups ($p = 0.5034$) (Supplemental Table 1). The adverse reaction after the first i.m. injection was caused by an i.m. injection of scopolamine/placebo, which was not associated with oral escitalopram. There were no significant differences for adverse reactions among the three groups after the first i.m. injection ($p = 0.3026$) (Supplemental Table 1).

Table 1. Demographic and clinical characteristics.

	Saline control[c] (*N*)	Low dose[c] (*n*)	High dose[c] (*n*)	*p* value
Participants	22	22	22	
Gender (M/F)	10/12	6/16	7/15	0.4300
Education				
Graduate school	11	10	18	0.1194
College graduate	8	8	3	
High school or less	3	4	1	
First episode (yes/no)	10/12	9/13	7/15	0.6413
Episodes of recurrence				
1 episode	5	6	4	0.9337[a]
2–3 episodes	4	3	2	
⩾4 episodes	1	0	1	
Duration of current episode (weeks)				
<8 weeks	4	6	5	0.4776
⩾8 weeks	18	16	16	
Any antidepressants at this episode	0	1	0	–
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	27.1 (7.0)	25.7 (5.3)	26.5 (5.6)	0.0736
Onset age (years)	25.0 (5.7)	22.8 (8.0)	25.3 (5.7)	0.4185
Duration of illness (years)	2.1 (2.9)	2.8 (5.4)	0.9 (2.0)	0.5711[b]
Clinical assessments				
Baseline HRSD17 total scores	24.5 (5.0)	25.7 (4.7)	25.4 (4.2)	0.6996
Baseline QIDS-SR total scores	14.5 (5.9)	16.4 (3.7)	16.1 (5.3)	0.4139
Baseline MADRS total scores	31.0 (7.9)	32.2 (5.8)	33.5 (6.4)	0.4613
Baseline CGI-S scores	4.7 (0.9)	5.1 (0.9)	5.1 (1.0)	0.3422

[a]Fisher's exact test.
[b]Kruskal–Wallis test.
[c]High dose, oral escitalopram + 0.3 mg i.m. scopolamine twice daily; low dose, oral escitalopram + 0.3 mg i.m. scopolamine once daily; saline control, oral escitalopram + i.m. saline twice daily;
CGI, Clinical Global Impressions scale; HRSD17, 17-item Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; QIDS-SR, Quick Inventory of Depressive Symptomatology Self Report 16-Item; SD, standard deviation.

Discussion

To the best of our knowledge, this is the first randomized, parallel-group, double-blind, controlled trial to systematically investigate the effects of i.m. injections of scopolamine as an adjunct to newly initiated treatment in patients with MDD. The study aims to assess whether this treatment combination could accelerate antidepressant efficacy and thus narrow the significant time gap in symptom amelioration seen with current oral antidepressant treatments.
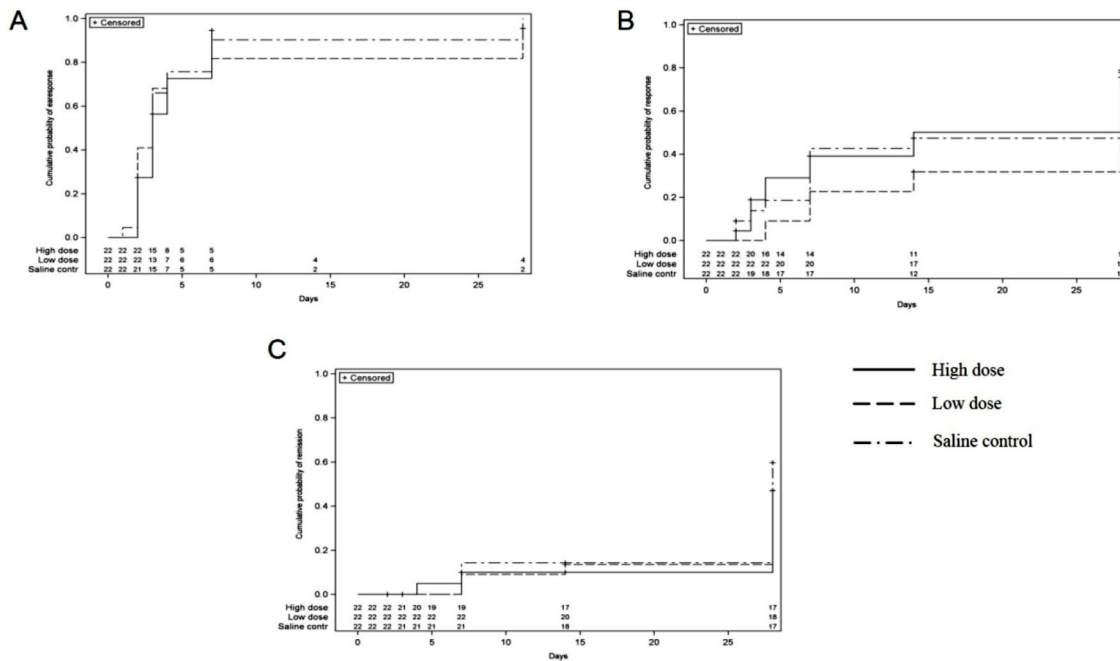
Figure 2. Time to early response, response and remission by Kaplan–Meier analysis. (a) Time to early response; (b) time to response (with number of subjects at risk); and (c) time to remission.

In this randomized, placebo-controlled trial of 66 subjects with MDD, a series of 3-day add-on scopolamine i.m. injections did not significantly shorten the effective time or improve depressive symptoms in patients with moderate to severe MDD compared to placebo. These negative results are not in line with previous studies of scopolamine for depression and suggest that the current study differs significantly from the injection strategies used in previous studies.[12] The change of injection method may be the primary reason why the results of this study were inconsistent with those of previous studies, which confirmed a rapid antidepressant effect using i.v. scopolamine (4 μg/kg). Whether scopolamine's utility as an antidepressant treatment can be achieved using other routes of administration remains unclear. Although blood scopolamine levels were not measured in this study, previous studies suggest that area under concentration-time curve (AUC) of i.m. injection of scopolamine is much lower than that induced by i.v. injection.[30] In our study, 0.3 mg scopolamine administered intramuscularly would have a bioavailability <2 μg/kg i.m.[15] Therefore, a possible explanation for our findings may be relative underdosing of scopolamine in this study compared to i.v. scopolamine.

Only one previous study used an i.m. injection. In that study, open-label administration of scopolamine (0.4 mg i.m.) to 10 depressed patients and 10 healthy controls before bedtime for three consecutive nights was found to have a small but significant antidepressant effect on the second morning of treatment.[18] Our combination of scopolamine injection and escitalopram is significantly different from the above study design, which is an important element in the inconsistency of the results. Combination therapy from the time of treatment initiation is increasingly being studied in the setting of MDD because of its tolerability profile, and results in significantly greater antidepressant response than monotherapy.[31–33]

In our study, add-on i.m. scopolamine use did not have a rapid antidepressant effect. Our findings are consistent with Lawrence Park's crossover trial study of 23 subjects with MDD; three i.v. injections of scopolamine did not significantly improve depressive or anxiety symptoms compared with placebo.[34] In another study, there was no clear effect of scopolamine patch on emotional cognition, verbal or working memory. This suggests that the effective dose of scopolamine available through the patch is too low to represent a viable antidepressant mechanism.[35] Therefore, the antidepressant effect of scopolamine is still controversial. A larger sample size and the

Table 2. Secondary efficacy outcomes of the change in total score of assessments from baseline to endpoint at week 4.

	High dose[a]	Low dose[a]	Saline control[a]
HRSD17 LS mean change (95% CI)	−8.0 (−9.0, −7.1)	−7.9 (−8.8, −7.0)	−8.3 (−9.2, −7.4)
HRSD17 LS mean difference from saline control group (95% CI)	0.2 (−1.0, 1.5)	0.4 (−0.9, 1.7)	
MARDS LS mean change (95% CI)	−9.1 (−10.3, −7.8)	−8.7 (−9.9, −7.5)	−9.5 (−10.7, −8.3)
MARDS LS mean difference from saline control group (95% CI)	0.4 (−1.4, 2.2)	0.8 (−0.9, 2.5)	
QIDS-SR-16 LS mean change (95% CI)	−4.1 (−4.8, −3.4)	−4.0 (−4.7, −3.4)	−4.5 (−5.1, −3.8)
QIDS-SR-16 LS mean difference from saline control group (95% CI)	0.3 (−0.6, 1.3)	0.4 (−0.5, 1.4)	
GAD-7 LS mean change (95% CI)	−3.1 (−3.8, −2.3)	−2.4 (−3.2, −1.7)	−2.1 (−2.9, −1.4)
GAD-7 LS mean difference from saline control group (95% CI)	−1.0 (−2.0, 0.1)	−3.0 (−1.4, 0.7)	
CGI-S LS mean change (95% CI)	−0.9 (−1.1, −0.8)	−1.0 (−1.1, −0.8)	−1.1 (−1.3, 1.0)
CGI-S LS mean difference from saline control group (95% CI)	0.2 (0.0, 0.4)	0.2 (−0.1, 0.4)	

[a]High dose, oral escitalopram + 0.3 mg i.m. scopolamine twice daily; low dose, oral escitalopram + 0.3 mg i.m. scopolamine once daily; saline control, oral escitalopram + i.m. saline twice daily.
CGI, Clinical Global Impressions scale; HRSD17, 17-item Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; QIDS-SR, Quick Inventory of Depressive Symptomatology Self Report 16-Item.

removal of confounding factors will be needed in the future to verify its efficacy.

In our study, the time to respond, the cumulative reduction rate and the cumulative remission rate were not significantly different in the control (placebo), low-dose and high-dose groups. There are three possible reasons for these negative results. First, a larger proportion of patients in this study were treatment-naive (60.6% in the current study) and only one patient had taken antidepressants prior to this episode, so they may be more sensitive to treatment. Although both treatment-naive and treatment-resistant groups respond significantly to scopolamine, the magnitude of response is greater for treatment-naive patients.[36] Second, the placebo response may be an important reason for the absence of statistically significant differences between the intervention and the placebo groups. The response to placebo in published trials of antidepressant medication for MDD is highly variable and often substantial, and has increased significantly in recent years.[37] Third, HRSD17 was used in this study as the primary outcome measure, but MADRS is more commonly used in other studies. The difference

in measurement tools may be one of the reasons for the inconsistent results.

In our study, the combination treatment group (high-dose group and low-dose group) did not achieve a greater antidepressant response than the placebo group, but the incidence of adverse reactions was higher. Two subjects from the high-dose group dropped out because of drug-related side effects. Intramuscular scopolamine produced blurred vision, dizziness, nausea, drowsiness and dry mouth. These side effects were relatively transient.

Our results have some limitations that should be acknowledged. First, the blood drug concentrations were not measured in our study and thus there is no objective basis for the exploration of dosage. Dose dependence in scopolamine's antidepressant effects may indicate that the current dose used was not sufficient and further studies are needed. Second, this was an augmentation study and augmentation assumes a different mechanism of action than the oral antidepressants patients were on during the study; thus, we cannot rule out the possibility that these

treatments share a final common mechanism. Third, the subject population was restricted to non-smokers due to the possible interaction with nicotinic and muscarinic receptors, both belonging to the cholinergic system. Therefore, our sample limits us in generalizing the findings to a wider age range of the population and to smokers. Fourth, the sample size included in this study is small. Future studies with larger sample sizes are therefore warranted. Fifth, it is possible that the adverse events associated with scopolamine may unblind the drug administration to patients, nurses and investigators.

Conclusion

This study evaluated the effects of scopolamine i.m. injections in patients with MDD. Contrary to study predictions, we found that scopolamine, compared to placebo (0.9% i.m. saline), was not associated with a significantly shorter time in antidepressant response.

The hypothesis generated by Janowsky *et al.* proposes that hypersensitivity of the cholinergic system plays a central role in the pathogenesis of mood disorders.[38] Determining an optimal schedule of administration and potential long-term use of scopolamine as an antidepressant agent requires further study, particularly as potential adverse effects include disturbed consciousness and delirium. Although the results of this study were negative, further studies are needed to explore the possible therapeutic effects of a range of additional doses and/or other forms of administration.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Table 3. Adverse events after randomization (SS).

	High dose[c] (N = 22)	Low dose[c] (N = 22)	Saline control[c] (N = 22)
AEs leading to discontinuation of study medications	2 (9.1)	0 (0)	0 (0)
Any AEs	20 (90.9)	22 (100.0)	14 (70.0)*
AEs happens over 2%			
Blurred vision[a]	10 (45.5)	8 (36.4)	0 (0)
Dizziness[a]	13 (59.1)	13 (59.1)	2 (9.1)
Somnolence[b]	3 (13.6)	2 (9.1)	2 (9.1)
Nausea[b]	9 (40.9)	7 (31.8)	9 (40.9)
Fatigue[b]	1 (4.5)	2 (9.1)	1 (4.5)
Drowsiness[a]	15 (68.2)	15 (68.2)	6 (27.3)
Dry mouth[a]	13 (59.1)	21 (95.5)	6 (27.3)
Anxiety[b]	4 (18.2)	2 (9.1)	0 (0)
Insomnia[b]	2 (9.1)	0 (0)	3 (13.6)
Tachycardia[b]	1 (4.5)	3 (13.6)	2 (9.1)
Any AEs by systems			
Nervous system disorders	34	33	10
Psychiatric disorders	5	1	4
Gastrointestinal disorders	24	29	19
Cardiac disorders	1	3	2
Eye disorders	1	2	1

*Fisher's exact test, *p* = 0.0024.
[a]Statistical difference among groups.
[b]No statistical difference among groups.
[c]High dose, oral escitalopram + 0.3 mg i.m. scopolamine twice daily; low dose, oral escitalopram + 0.3 mg i.m. scopolamine once daily; saline control, oral escitalopram + i.m. saline twice daily.
AEs, adverse events.

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Supplemental material
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