Oral Scopolamine Augmentation in Moderate to Severe Major Depressive Disorder: A Randomized, Double-Blind, Placebo-Controlled Study

Danial Khajavi, MD; Mehdi Farokhnia, MD; Amirhossein Modabbernia, MD; Mandana Ashrafi, MD; Seyed-Hesammedin Abbasi, MD; Mina Tabrizi, MD; and Shahin Akhondzadeh, PhD

ABSTRACT

Objective: To evaluate the antidepressant effect of oral scopolamine as an adjunct to citalopram.

Method: In this randomized double-blind placebo-controlled study, patients were assessed in the outpatient clinics of 2 large hospitals from November 2011 to January 2012. Forty patients (18–55 years) with major depressive disorder (*DSM-IV-TR* criteria) and 17-Item Hamilton Depression Rating Scale (HDRS) score ≥ 22 were randomly assigned to scopolamine hydrobromide (1 mg/d) (n = 20) or placebo (n = 20) in addition to citalopram for 6 weeks. HDRS score was measured at baseline and days 4, 7, 14, 28, and 42. The primary outcome measure was HDRS score change from baseline to week 6 in the scopolamine group versus the placebo group. Response was defined as ≥ 50% decrease in HDRS score; remission, as HDRS score ≤ 7.

Results: Augmentation with scopolamine was significantly more effective than placebo ($F_{1,38} = 5.831$, $P = .021$). Patients receiving scopolamine showed higher rates of response (65%, 13/20 at week 4) and remission (65%, 13/20 at week 6) than the placebo group (30%, 6/20 and 20%, 4/20, respectively; $P = .027$, $P = .004$, respectively). Patients in the scopolamine group showed higher rates of dry mouth, blurred vision, and dizziness than the placebo group.

Conclusions: Oral scopolamine is a safe and effective adjunct for treatment of patients with moderate to severe major depressive disorder.

Trial Registration: Iranian Registry of Clinical Trials identifier: IRCT201201181556N31

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Corresponding author: *Prof. Shahin Akhondzadeh, PhD, Psychiatric Research Center, Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, South Kargar St, Tehran 13337, Iran (s.akhond@neda.net).*

Relatively large numbers of patients do not respond to antidepressants; therefore, augmentative strategies are important aspects of depression treatment.[1–3] Most of these strategies focus on the recently proposed mechanisms for major depressive disorder (MDD). These mechanisms include impaired neuroprotection, neuroinflammation, and disturbances in neurotransmitter systems other than serotonin, dopamine, and norepinephrine.[1] Janowsky and colleagues[4,5] were one of the first groups to propose adrenergic-cholinergic imbalance as a mechanism underlying MDD in 1972. This hypothesis was nearly ignored at that time due to a lack of response to anticholinergic drugs, probably because of small sample size and dosage of the drug.[6] However, much indirect evidence for involvement of the cholinergic pathway in MDD was discovered even then and thereafter.[6–12] Increased cholinergic activity is associated with depressive-like behavior in animals and humans, whereas decreased activity of the cholinergic system may be related to depressive symptom reduction.[4,5,13] In addition, tricyclic antidepressants (TCAs), which are potent antidepressants, are also potent antimuscarinic agents.[14] Moreover, genetic polymorphisms in the acetylcholine receptor are associated with risk of MDD.[11,12] Antidepressant efficacy of anticholinergic drugs can also be explained by association of rapid eye movement (REM) sleep abnormalities and MDD. Abnormalities of REM sleep such as shortening of REM latency, longer duration of first REM period, and heightening of REM density are commonly seen in patients with MDD.[15] Interestingly, muscarinic agonists have been shown to increase REM sleep, and muscarinic antagonists have been shown to counteract this effect.[16] Intriguingly, selective REM sleep deprivation is considered an effective strategy for reduction of depressive symptoms.[15] An association has been noted between reduced time spent in REM sleep induced by amitriptyline (a TCA with significant anticholinergic properties) and clinical improvement in symptoms of patients with MDD.[17]

In recent years, some animal and human studies[13,18–20] have provided more direct evidence for antidepressant effects of an anticholinergic agent, scopolamine. The first evidence of antidepressant efficacy of scopolamine was found in 1991 by Gillin et al[21] in a pilot study of 10 moderately depressed patients. They showed a small but statistically significant decrease in depression score following administration of intramuscular scopolamine. No further attempt was made to address the antidepressant effect of this drug in more detail until 2006 when, while studying the cognitive effects of intravenous scopolamine, Furey and Drevets[18] incidentally found significant antidepressant properties of this drug. Subsequently, they designed 2 crossover randomized controlled trials,[18,20] both of which showed a significant and rapid antidepressant effect of intravenous scopolamine compared with placebo.

Because of inadequate response and remission rates seen with routine antidepressant drugs, there is an increasing interest in combining drugs with antidepressant efficacy from the beginning of the treatment.[22–24] Accordingly, assessment of the efficacy of scopolamine augmentation might be

of particular value due to the robust and rapid effect it has shown in previous studies. Furthermore, previous studies only addressed the effect of IV scopolamine, which may be difficult to use in the clinical (particularly outpatient) setting. Therefore, we designed the present study to assess the tolerability and efficacy of oral scopolamine as an adjuvant therapy in patients with moderate to severe MDD.

Clinical Points

- Oral scopolamine hydrobromide augmentation of citalopram was more effective in treating moderate to severe major depressive disorder than was citalopram monotherapy.
- Scopolamine was well tolerated in patients with major depressive disorder.

METHOD

Trial Design

Our study was a 2-center, randomized, placebo-controlled, double-blind, parallel-group study conducted in Tehran, Iran. (Iranian Registry of Clinical Trials: IRCT 201201181556N31).

Changes to Trial Design

Based on the primary trial protocol, we planned to assess the patients at weeks 2, 4, and 6. Subsequently, the trial group decided to consider 2 additional earlier timepoints with the intent to assess the tolerability of scopolamine early in the course of the trial. Therefore, 2 additional visits at days 4 and 7 were added to the follow-up plan. This change in the protocol was amended at the beginning of the study.

Patients

Patients were assessed in the outpatient clinics of Roozbeh Psychiatric Hospital (a tertiary referral center affiliated with Tehran University of Medical Sciences) and National Iranian Oil Company Central Hospital from November 20, 2011, to January 20, 2012. Inclusion criteria were age of 18 to 55 years, diagnosis of MDD (*DSM-IV-TR* criteria), and 17-Item Hamilton Depression Rating Scale (HDRS)[25] score of ≥ 22 and score of ≥ 2 on item 1 of the HDRS. Exclusion criteria were receiving psychotropic agents, alternative medicine, or psychotherapy within 4 weeks; psychosis; other disorders on *DSM* Axis I; substance abuse or dependence within 1 year; electroconvulsive therapy within 8 weeks; high risk of suicide (score ≥ 2 on the suicide item of HDRS or clinical judgment); pregnancy; lactation; serious or life-threatening disease; cognitive impairment (based on subjective complaints and clinical judgment); hypertension; smoking; cardiovascular disease; thyroid disease; glaucoma (narrow-angle); myasthenia gravis; prostatic hyperplasia; hypersensitivity to anticholinergic drugs; and hepatic or renal dysfunction.

Screened patients underwent a thorough history and clinical and electrocardiographic examination for presence of any disease listed in the exclusion criteria. The patients underwent an eye examination to exclude glaucoma. Moreover, all male patients who had symptoms of prostatic hyperplasia or were > 40 years of age underwent a digital rectal examination to rule out prostatic hyperplasia. The patients were not allowed to receive psychotherapy during the course of the study. The protocol was approved by the Institutional Review Board (IRB) of Tehran University of Medical Sciences (grant no. 10349). 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 subjects and their legally authorized representatives signed a written informed consent form.

Interventions

Subjects randomly received either scopolamine hydrobromide (containing 0.5 mg active ingredient) tablets (ACER, Tehran, Iran) twice daily plus citalopram or placebo (with the same appearance as scopolamine) plus citalopram for 6 weeks. The dosage of citalopram was 20 mg/d for the first week and then 40 mg/d (for all patients) for the subsequent 5 weeks. Tablets were dispensed every 2 weeks, and compliance was assessed using pill count.

Outcomes

Depressive symptoms were rated at baseline and days 4, 7, 14, 28, and 42 using HDRS. The primary outcome measure was HDRS score change from baseline to week 6 in the scopolamine versus the placebo group. Early improvement (at least 20% reduction in HDRS score at the end of the first and second weeks),[26] score reduction (at each session), response rates (at least 50% decrease in the HDRS score at week 4 and 6), and remission rates (HDRS score ≤ 7) at the end of the trial were also compared between the 2 groups.[27] At each visit during the course of the trial, all participants were systematically asked about the presence of adverse events using a checklist. Three raters (with an interrater reliability > 85%) were responsible for assessment of symptoms and side effects.

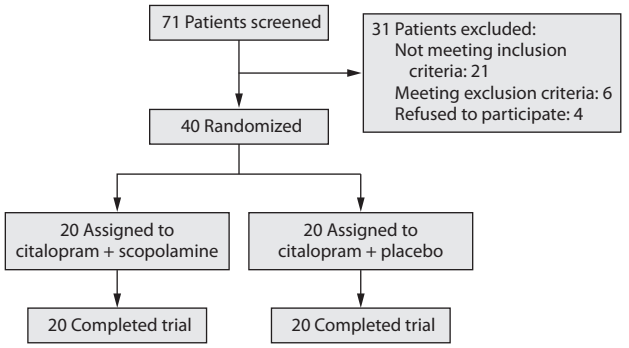
Sample Size

Using a standard deviation of 3.5 on the HDRS, assuming a clinically significant difference of 3.5 on the scale, a power of 80%, and 2-sided significance of 5%, a minimal sample size of 32 was calculated. Assuming an attrition rate of 20%, a sample size of 40 was planned.

Randomization, Allocation Concealment, and Blinding

A computerized random number generator was used for randomizing participants in a 1:1 ratio in blocks of 4. Allocation was concealed using sequentially numbered, opaque, sealed, and stapled envelopes. The patients, the clinicians who referred the patients, and the psychiatrists who rated the patients and administered the medication were blind

Figure 1. Flow Diagram of the Trial



to allocation. Different persons were responsible for random allocation and rating of the study subjects.

Statistical Analysis

IBM SPSS Statistic 19.0.0 (IBM Corporation, Armonk, New York) was used for data analysis. Continuous variables were reported as mean ± SD, and categorical variables were reported as number (%) of patients. We used 2-factor repeated-measures analysis of variance (ANOVA) to compare the score change between the 2 groups. Treatment group and HDRS score at 6 timepoints were assigned as between-subject and within-subject factors, respectively. Whenever Mauchly's test of sphericity was significant, we reported the results of the Greenhouse-Geisser correction. Analysis of covariance controlling for baseline HDRS scores was used for comparison of the change (at each timepoint) in HDRS score between the placebo and scopolamine arms. Pearson χ^2, Fisher exact test, and risk ratios (RRs) with 95% confidence intervals (CIs) were used for comparison of proportions (percentage of early improvers at weeks 1 and 2, responders at weeks 4 and 6, remitters at week 6, and adverse events) between the 2 groups. We also calculated Cohen *d* size by dividing the mean difference of the 2 groups at the end of the sixth week by their pooled standard deviation. A *P* value of < .05 was considered statistically significant in all analyses.

RESULTS

Patient Characteristics

Seventy-one patients were screened for eligibility criteria, of whom 40 patients were assigned to either scopolamine plus citalopram (n = 20) or placebo plus citalopram (n = 20) (Figure 1). Baseline characteristics of the participants are summarized in Table 1. No attrition or serious adverse events were reported during the course of the study. Baseline HDRS scores did not differ between the 2 groups (mean ± SD for scopolamine, 24.5 ± 2.2; for placebo, 24.2 ± 2.3; $P = .725$). Complete HDRS scores were available for all 40 patients at the end of the study.

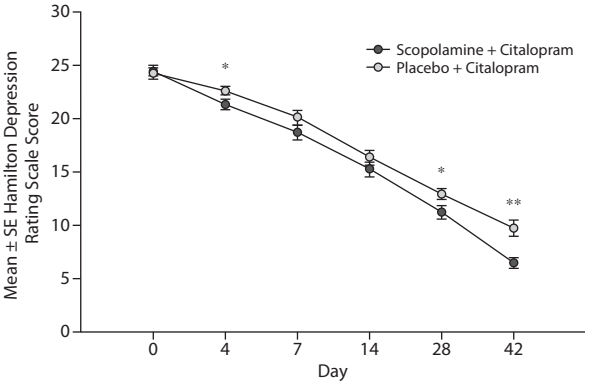
Outcome

Two-factor ANOVA with repeated measures showed significantly better results in scopolamine-treated patients

Table 1. Baseline Characteristics of Patients Receiving Citalopram Augmented With Scopolamine or Placebo

Variable	Citalopram Plus Scopolamine Group (n = 20)	Citalopram Plus Placebo Group (n = 20)
Age, mean ± SD, y	37.8 ± 6.7	36.6 ± 6.8
Sex, n (%) female	12 (60)	13 (65)
Married, n (%)	6 (30)	5 (25)
University education, n (%)	6 (30)	6 (30)
Baseline weight, mean ± SD, kg	68.7 ± 9.2	70.1 ± 8.9
Duration of current episode, mean ± SD, mo	4.5 ± 9.5	5.3 ± 12.3
No. of previous episodes, mean ± SD	3.75 ± 0.76	3.62 ± 0.81
Total duration of episodes, mean ± SD, mo	30.1 ± 9.7	33.1 ± 11.4
Medication history in the previous episode, n (%)		
Fluoxetine	7 (35)	4 (20)
Citalopram	6 (30)	7 (35)
Sertraline	5 (25)	7 (35)
Venlafaxine	2 (10)	1 (5)
Paroxetine	0 (0)	1 (5)
Baseline Hamilton Depression Rating Scale score, mean ± SD	24.5 ± 2.2	24.2 ± 2.3

Figure 2. Results of 2-Factor Repeated-Measures Analysis of Variance



*$P < .05$, **$P < .01$.

than in the placebo group ($F_{1,38} = 5.831$, $P = .021$) (Figure 2). Using the Greenhouse-Geisser correction, the effect was also significant for time ($F_{2.731,103.759} = 345.034$, $P < .001$) and time-treatment interaction ($F_{2.731,103.759} = 2.949$, $P = .04$). At the end of the sixth week, patients in the scopolamine group experienced a mean of 73.8% reduction in their HDRS score, whereas this value was 59.3% in patients in the placebo group ($F_{1,37} = 12.518$, $P = .001$ after controlling for baseline score). The scopolamine group experienced significantly greater reduction in HDRS score at days 4, 28, and 42 than the placebo group (Table 2). An effect size of 0.9 (Cohen *d*; 95% CI, 0.25–1.55) was calculated for the difference in score reduction at week 6 between the 2 groups (Table 2).

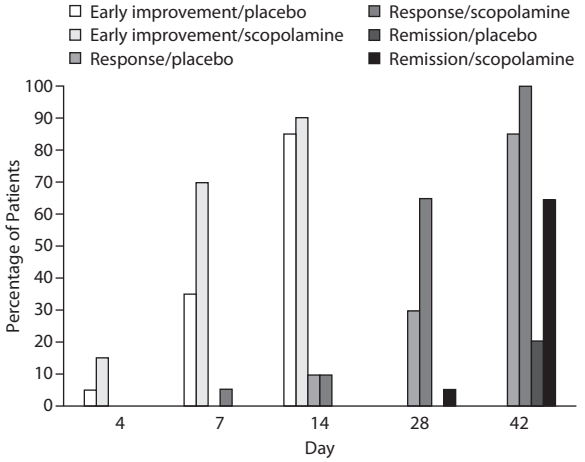
Significantly more patients in the scopolamine group (14/20, 70%) experienced 20% reduction in HDRS score by week 1 than in the placebo group (7/20, 35%) (RR [95% CI] = 0.487 [0.247–0.959], $P = .027$). In the second week,

Table 2. Comparison of Hamilton Depression Rating Scale (HDRS) Score Changes Between the 2 Groups Using Analysis of Covariance

	Citalopram Plus Scopolamine, Mean[a] (95% CI)	Citalopram Plus Placebo, Mean[a] (95% CI)	Mean Difference: Scopolamine – Placebo (95% CI)	$F_{1,37}$	P	Cohen d (95% CI)
Change from baseline[b] to day 4	−3.1 (−3.9 to −2.4)	−1.7 (−2.5 to −0.9)	−1.4 (−2.5 to −0.4)	7.351	.010	0.80 (0.15 to 1.44)
Change from baseline to day 7	−5.7 (−7.1 to −4.1)	−4.2 (−5.6 to −2.8)	−1.5 (−3.5 to 0.5)	2.376	.132	0.50 (−0.13 to 1.12)
Change from baseline to day 14	−9.2 (−10.5 to −7.8)	−8.0 (−9.3 to −6.7)	−1.2 (−3.0 to 0.7)	1.622	.211	0.41 (−0.22 to 1.03)
Change from baseline to day 28	−13.2 (−14.3 to −12.0)	−11.4 (−12.6 to −10.3)	−1.7 (−3.4 to −0.1)	4.576	.039	0.62 (−0.02 to 1.25)
Change from baseline to day 42	−17.9 (−19.3 to −16.6)	−14.7 (−16.0 to −13.4)	−3.2 (−5.1 to −1.4)	12.178	.001	0.90 (0.25 to 1.55)

[a]Mean values of each group represent the mean after adjusting for baseline score.
[b]Baseline HDRS scores (mean ± SD) were 24.5 ± 2.2 in the scopolamine group and 24.2 ± 2.3 in the placebo group.

Figure 3. Frequency of Early Improvement (≥ 20% reduction in HDRS score within 2 weeks), Response (≥ 50% reduction in HDRS score), and Remission (HDRS score ≤ 7) During Augmentation of Citalopram With Scopolamine vs Placebo



Abbreviation: HDRS = Hamilton Depression Rating Scale.

most of the patients in both groups had reached the criteria for early improvement (18/20, 90% vs 17/20, 85%; RR [95% CI] = 0.810 [0.366–1.789], P = .633). By the fourth week, 13 (65%) of patients in the scopolamine group experienced 50% reduction in their HDRS scores compared with 6 (30%) of the patients in the placebo group (RR [95% CI] = 0.474 [0.229–0.981], P = .027). All patients in the scopolamine group (0.229–0.981) and most patients in the placebo group (20/20; 100%) had reached 50% reduction in their HDRS scores by week 6 (RR [95% CI] = 0.459 [0.324–0.652], P = .231). However, the remission rate at the sixth week was significantly higher in patients in the scopolamine group than in patients in the placebo group (13/20, 65% vs 4/20, 20%; RR [95% CI] = 0.338 [0.138–0.831], P = .004). A comparison of improvement, remission, and response rates between the 2 groups is provided in Figure 3.

Adverse Effects

Nine adverse events were recorded throughout the study (Table 3). Dry mouth, dizziness, and blurred vision were more common in the scopolamine group (50%, 40%, and 40%, respectively) than in the placebo group (20%, 15%, and 15%, respectively) (P = .04, P = .07, and P = .07, respectively). No serious cardiovascular event occurred during the study.

Table 3. Frequency of Side Effects in the Study Groups, n (%)

Side Effects	Citalopram Plus Scopolamine	Citalopram Plus Placebo
Dry mouth[a]	10 (50)	4 (20)
Blurred vision[a]	8 (40)	3 (15)
Dizziness[a]	8 (40)	3 (15)
Drowsiness	7 (35)	5 (25)
Nausea	3 (15)	3 (15)
Headache	3 (15)	2 (10)
Palpitation	2 (10)	3 (15)
Nervousness	2 (10)	2 (10)
Vertigo	2 (10)	2 (10)

[a]Dry mouth, blurred vision, and dizziness were more common in the scopolamine than in the placebo group (P = .04, P = .07, P = .07, respectively).

No other serious adverse events were recorded in the course of the study.

DISCUSSION

In the present study, we showed that oral scopolamine can be used as an effective and safe augmentative strategy in patients with moderate to severe MDD. Baseline characteristics of the patients were similar in the 2 groups and thus could not explain the observed difference in efficacy between the 2 treatment regimens. Moreover, to the best of our knowledge, there is no known interaction between scopolamine and citalopram, supporting that the observed difference between the 2 groups was due to an add-on effect of scopolamine rather than increased plasma concentrations of citalopram.

A recent study of the antidepressant effect of intraperitoneal scopolamine in mice showed that this drug decreases immobility time in tail suspension test and forced swimming test without learning and memory impairment.[13] A group of researchers at the National Institute of Mental Health provided substantial evidence for the effect of intravenous scopolamine monotherapy in patients with unipolar depression and bipolar depression.[18] First, they determined the optimal dose of the drug in a small study of 8 patients. Subsequently, they designed a randomized double-blind crossover study of 19 patients who were randomly assigned to receive either a placebo/scopolamine or a scopolamine/placebo sequence. They showed that intravenous scopolamine produced both rapid and lasting antidepressant effects compared with placebo. Later, they replicated their findings in a larger study.[19,20] In our study, scopolamine-augmented citalopram provided

an additional effect size of 0.9 over citalopram, which is comparable to monotherapy-placebo comparisons in the literature (0.5–1.1).[28] In their study, Drevets and Furey[20] showed effect sizes of 1.2–1.7 for intravenous scopolamine compared with placebo. Taken together, these findings suggest that scopolamine shows substantial antidepressant efficacy when used either alone or in an augmented regimen.

Despite a growing body of evidence on the antidepressant efficacy of scopolamine, the precise mechanism of action for this drug in MDD remains to be elucidated. Evidence for involvement of the hypersensitive cholinergic system (or hypercholinergic state) in MDD,[8,9,29,30] beneficial effects of sleep deprivation on sleep symptomatology,[15] association of depression with polymorphisms in type 2 muscarinic receptor gene,[11,12] and anticholinergic properties of TCAs[14] link muscarinic receptors with MDD and thus with the antidepressant mechanism of scopolamine. Alteration in type 2 and 3 muscarinic receptors has been reported in postmortem brain of patients with MDD and bipolar disorder.[31] Of note, scopolamine has high affinity for type 3 muscarinic receptors.[18,19] Moreover, interaction of scopolamine with some glutamate receptors might also play a role in the antidepressant mechanism of action of this drug. Hyperactivity of the glutamatergic system has been linked to pathophysiology of MDD.[32–34] Scopolamine, like several other antidepressants, is capable of decreasing glutamatergic transmission, possibly via decreasing *N*-methyl-D-aspartate receptor function and/or expression.[35–37]

Combination therapy from the time of treatment initiation is increasingly being studied in the setting of MDD because it is well tolerated and results in significantly greater antidepressant response than monotherapy.[22–24] In our study, scopolamine augmentation of one group from the beginning was associated with greater score reduction and thus higher response and remission rates than in the placebo group. By week 6, 65% of patients receiving a scopolamine-augmented regimen compared with 20% of patients receiving citalopram alone achieved remission. Remission rates in the citalopram monotherapy group of our study were comparable to the remission rates of 10%–40% reported in trials of citalopram with 4–12 weeks' duration.[38] Of note, augmentation with scopolamine resulted in a remission rate (65%) that was higher than the rates reported in most studies in which the "augmentation from the initiation" strategy was used (43%–58% for different combinations).[22–24,39]

In the present study, rapid action of oral scopolamine was evidenced by a small but significant difference in score reduction between the 2 groups by day 4. However, this score-reducing effect of scopolamine subsided in subsequent visits until the fourth week, and a clinically significant difference (defined as at least a 3-point score difference according to National Institute for Clinical Excellence criteria[40]) was evident by week 6. Drevets and Furey have shown both rapid and long-lasting action of intravenous scopolamine.[18,20] The differences between the designs of the 2 studies may explain the differences observed between the findings. Importantly, Drevets and Furey used scopolamine monotherapy, whereas we used scopolamine in an augmentative regimen. Therefore, the larger difference observed by Drevets and Furey compared with our study possibly reflects the use of an effective antidepressant, citalopram, in the placebo arm of our study. In addition, the higher bioavailability of intravenous scopolamine than oral scopolamine probably explains part of this difference.

Our study had some limitations. First, we did not measure cognitive side effects of scopolamine, although in similar previous studies,[18–21] little evidence of cognitive dysfunction has been found. Moreover, as previously noted, scopolamine had high affinity for the type 3 muscarinic receptor, and the knockout murine model for this receptor does not appear to show cognitive impairments.[41] Second, our sample limited us in generalization of our findings to the extremes of age and to patients with bipolar depression.

CONCLUSIONS

We showed that adding oral scopolamine to the antidepressant regimen in patients with moderate to severe MDD is an effective and safe strategy to achieve high response and remission rates. Nevertheless, long-term efficacy and safety of scopolamine, as well as its optimal dosing, require further investigation.

Drug names: citalopram (Celexa and others), fluoxetine (Prozac and others).

Author affiliations: Psychiatric Research Centre, Roozbeh Hospital (Drs Khajavi, Farrokhnia, Modabbernia, Ashrafi, and Akhondzadeh) and Department of Medical Genetics, Faculty of Medicine (Dr Tabrizi), Tehran University of Medical Sciences; and Family Health Research Center, Iranian Petroleum Industry Health Research Institute, National Iranian Oil Company Central Hospital (Dr Abbasi), Tehran, Iran.

Potential conflicts of interest: None reported.

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Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Oral Scopolamine Augmentation in Moderate to Severe Major Depressive Disorder: A Randomized, Double-Blind, Placebo-Controlled Study

Author(s): Danial Khajavi, MD; Mehdi Farrokhnia, MD; Amirhossein Modabbernia, MD; Mandana Ashrafi, MD; Seyed-Hesammedin Abbasi, MD; Mina Tabrizi, MD; and Shahin Akhondzadeh, PhD

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List of Supplementary Material for the article

1. eTable 1 CONSORT 2010 Checklist of Information to Include When Reporting a Randomised Trial

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3,4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	6
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	9(figure 1)
	13b	For each group, losses and exclusions after randomisation, together with reasons	9
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	9
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Table 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	10, figure 2
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	10
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11,12,13,14
Other information			
Registration	23	Registration number and name of trial registry	15
Protocol	24	Where the full trial protocol can be accessed, if available	15
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	15

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.