# Replication of Scopolamine's Antidepressant Efficacy in Major Depressive Disorder: A Randomized, Placebo-Controlled Clinical Trial

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**Background:** We previously reported that intravenous (IV) scopolamine administration produced rapid and robust antidepressant effects in a sample consisting of both unipolar and bipolar depressives. The present study aimed to replicate this finding in an independent sample limited to unipolar depressives.

**Methods:** Outpatients with major depressive disorder (MDD; $n = 23$; 22 were included in analyses) participated in a double-blind, placebo-controlled, crossover trial. Subjects were randomized into either a P/S or S/P sequence (P = block of three placebo sessions; S = block of three scopolamine sessions; [4.0 μg/kg IV]). Sessions occurred 3 to 5 days apart, such that time spent in each block lasted 1.5 to 2 weeks and the interval between blocks was 3 to 5 days. The Montgomery-Asberg Depression Rating Scale (MADRS) served as the primary outcome measure.

**Results:** Following the initial block, the group receiving scopolamine first (S/P) showed a 32% reduction in MADRS scores ($p < .001$), which exceeded the corresponding change of 6.5% under placebo (P/S; $p = .009$), confirming the a-priori hypothesis. Improvement was significant at the first evaluation that followed scopolamine administration ($p = .011$). In Block 2, the P/S group showed a 53% reduction in MADRS scores ($p = .001$) following scopolamine versus placebo, whereas the reduction seen in S/P subjects who received scopolamine during Block 1 persisted as they received placebo during Block 2. Scopolamine induced drowsiness, blurred vision, dry mouth, light-headedness, and reduced blood pressure, which were sufficiently well tolerated that no subject dropped out because of side effects.

**Conclusions:** These results replicate previous finding that scopolamine produces a rapid and robust antidepressant response.

**Key Words:** Anticholinergic, antimuscarinic, mood disorders, treatment

The need to develop improved antidepressant treatments that more quickly and effectively treat major depression remains critical (1). We reported previously the results of a clinical trial conducted at the National Institute of Mental Health (NIMH) showing that the muscarinic cholinergic receptor antagonist scopolamine exerted antidepressant effects in depressed patients ($N = 18$) with either major depressive disorder (MDD; $n = 9$) or bipolar disorder ($n = 9$) (2). In this double-blind, placebo-controlled, crossover trial, subjects underwent multiple sessions in which they received intravenous (IV) infusions of placebo or scopolamine (4 μg/kg). Individuals were randomized into either a P/S or S/P sequence, in which the former received placebo followed by scopolamine and the latter received scopolamine followed by placebo. The P/S group showed no significant improvement during the placebo series but significant reductions in ratings of depression and anxiety severity following the administration of scopolamine compared with placebo. The S/P group also showed significant reductions in depression and anxiety ratings following scopolamine, and these effects persisted throughout the subsequent placebo series, well beyond the expected duration of scopolamine's direct action at muscarinic receptors. Moreover, in both the P/S and S/P subgroups, improvement was significant at the first evaluation that followed scopolamine administration (i.e., 3–5 days following the initial administration), suggesting that the antidepressant responses to scopolamine was relatively rapid.

In the current study, we sought to replicate the finding that scopolamine exerts antidepressant effects in an independent subject sample. Because the original sample consisted of both unipolar and bipolar cases, we recognized the need to replicate the findings independently in each mood disorder. This study thus limited recruitment to MDD subjects.

## Methods and Materials

### Participants

Volunteers between 18 and 45 years of age evaluated at the NIMH outpatient clinic were assessed for eligibility if they were nonsmokers and met DSM-IV (3) criteria for recurrent MDD on the basis of an unstructured interview conducted by a psychiatrist and the Structured Clinical Interview for DSM-IV. Exclusion criteria included exposure to psychotropic drugs or other medications likely to affect cholinergic function within 3 weeks (8 weeks for fluoxetine), serious risk of suicide, delusions or hallucinations, lifetime history of substance dependence or substance abuse within 1 year, medical or neurological disorders, narrow-angle glaucoma, hypersensitivity to anticholinergic agents, hepatic dysfunction, electrolyte disturbance, HIV or hepatitis viral infection, or weight greater than 125 kg. Pregnant or nursing women were also excluded. Subjects provided written informed consent as approved by the NIMH Institutional Review Board.

### Study Design

During each of seven sessions, subjects received a 15-min IV infusion of either a placebo saline solution or scopolamine (4.0 μg/kg). A single-blind, lead-in session was used in which all subjects received a placebo infusion. As psychiatric assessments

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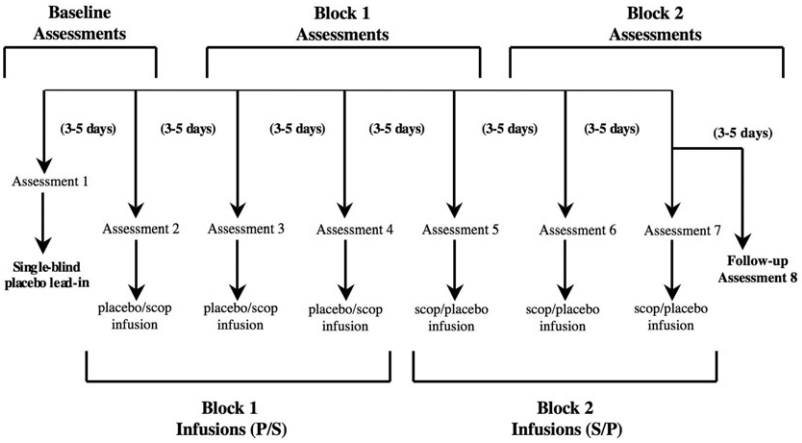


**Figure 1.** Study blocked experimental design reflecting infusion series and assessment sessions for each of the two randomized patient groups. P/S reflected the infusion series of placebo followed by scopolamine; S/P indicated scopolamine followed by placebo.

were obtained before infusions, the lead-in placebo in Session 1 allowed a second baseline assessment to be obtained immediately before the Session 2 infusion. Subsequently, individuals were randomized into either a P/S or S/P double-blind, placebo-controlled, crossover design in which P constituted a block of three placebo sessions and S a block of three scopolamine sessions (Figure 1). A follow-up evaluation provided the final assessment following Session 7 (i.e., "Assessment 8"). Randomization sequences were determined by the National Institutes of Health outpatient pharmacy and assigned by subject number at consenting. Sessions were scheduled 3 to 5 days apart.

Sample size was determined using power calculations involving data obtained from our initial study, where we observed a group difference in Montgomery-Asberg Depression Rating Scale (MADRS) scores at the end of study Block 1 of 17.4 points. If we predicted an improvement of one half the magnitude of that seen in the earlier study and the same group variance, a sample size of 11 per group provided power of 80% for alpha = .05.

### Assessment

Before each infusion, depression severity was rated using the MADRS (4), anxiety symptoms were rated using the Hamilton Anxiety Rating Scale (HARS) (5), the development of hypomanic symptoms was assessed using the Young Mania Rating Scale (YMRS) (6), and the Clinical Global Impressions (CGI) (4) scale was applied as a global assessment of illness severity. To evaluate within-session changes in mood, visual analogue scales (VAS; components included happy, sad, drowsy, irritated, alert, anxious, and restless) were administered at baseline and 20, 60, 120, and 150 min following initiation of the infusion, and the Profile of Mood State (POMS) (7) was administered at baseline, 20, 60, and 150 min postinfusion. Blood pressure and heart rate were measured at baseline, at 15-min intervals for 60 min following the infusion start, and at 30-min intervals for the remainder of the session using a Dynamap Vital Signs Monitor (Critikon, Tampa, FL).

### Outcome Measures

The antidepressant response was evaluated by assessing changes in MADRS scores. Using conventional criteria (8), patients were characterized as achieving full response (≥50% reduction in MADRS score from baseline), partial response (<50% but ≥25% reduction), or nonresponse (<25% reduction). Patients achieving remission (posttreatment MADRS score ≤10) were also identified. Secondary outcome measures included the HARS, CGI, VAS, and POMS. The VAS and POMS scores were assessed by comparing the mean ratings for each time point across the drug or placebo sessions.

### Data Analysis

A group (P/S vs. S/P)-by-assessments repeated-measures analysis of variance (ANOVA) was performed to evaluate overall group differences in the MADRS. To provide a balanced design, MADRS data were separated into a baseline block (Assessments 1 and 2), the first and last measures of Block 1 (Assessments 3 and 5), and Block 2 (Assessments 6 and 8). The a-priori hypothesis that scopolamine would exert antidepressant effects relative to placebo was tested primarily using the group-by-block ANOVA. The a-priori hypothesis that the antidepressant effect of scopolamine is rapid was tested using ANOVA limited to the results for the first assessment that followed the first exposure to scopolamine versus the corresponding change under placebo. Between- and within-group $t$ tests were used in planned comparisons to identify where significant effects occurred in the presence of significant overall ANOVAs. Post hoc tests were performed to assess the significance of changes in the secondary outcome measures (HARS, CGI-I, VAS, POMS). All $p$ values reported are two-tailed.

## Results

### Subjects

The passage of subjects through the phases of this clinical trial is detailed in Figure S1 in Supplement 1. Of 42 eligible patients, 19 were assessed for eligibility but were excluded for not meeting entrance criteria ($n = 6$) or declining to participate ($n = 13$), so 23 were randomized into the study. One subject dropped out after randomization but before Session 1, so this subject did not contribute any data to the analysis. Twenty-one subjects completed the trial as intended, and another subject dropped out after Session 6 because of nonresponse; this subject's data were included in the analysis on the basis of last observation carried forward. Thus, 22 patients received the intended treatment and were included in all analyses, 11 of whom were randomized into the P/S group and 11 into the S/P group. In three cases who completed all seven infusions, the follow-up evaluations could not be obtained for the assessment following Session 7 (i.e., Assessment 8), so analyses were performed using the last observation (from Session 7) carried forward (LOCF). Group characteristics are summarized in Table 1. The S/P and P/S groups did not differ in MADRS or HARS scores at baseline ($F < .10$, $p > .80$).

**Table 1.** Patient Characteristics at Baseline

| | P/S Group ($n$ = 11) (Mean ± SD) | S/P Group ($n$ = 11) (Mean ± SD) |
|---|---|---|
| Mean Age ± SD | 30 ± 7.0 | 33 ± 7.1 |
| Patient Sex | 7 F/4 M | 5 F/6 M |
| Mean MADRS ± SD | 31 ± 6.5 | 30 ± 3.7 |
| Mean HARS ± SD | 18 ± 8.2 | 20 ± 9.2 |
| Chronic Illness | 8/11 | 5/11 |
| Comorbid Anxiety Disorder | 3/11 | 5/11 |
| Unresponsive to Treatment | 3/11 | 3/11 |

In the S/P group ($n$ = 11; 5 women; four African American, six Caucasian, one Hispanic; mean age = 33 ± 7.1 years), 5 of 11 patients were chronically ill (current episode duration >2 years), 5 of 11 had a comorbid anxiety disorder, and 3 of 11 were unresponsive to previous treatment. In the P/S group ($n$ = 11; 7 women; four African American, six Caucasian, one Hispanic; mean age = 30 ± 7.0), 8 of 11 patients were chronically ill, 3 of 11 had a comorbid anxiety disorder, and 3 of 11 were unresponsive to previous treatment, on the basis of the response to the most recent therapeutic trial of a conventional antidepressant agent. In total, on the basis of their history of having nonresponse to previous treatment, chronicity, or a comorbid anxiety disorder (38–41), 16 of 22 patients had a poor prognosis for response to treatment, including seven in the S/P group and nine in the P/S group.

HARS, Hamilton Anxiety Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; P/S, subjects randomized to receive placebo in Study Block 1 and scopolamine in Block 2; S/P, subjects randomized to receive scopolamine in Block 1 and placebo in Block 2.

## Adverse and Side Effects

Scopolamine was well-tolerated and no medically serious adverse events were encountered. Side effects reported under scopolamine and placebo conditions are listed in Table 2. Heart rate, systolic blood pressure (BP), and diastolic BP decreased following scopolamine infusion relative to placebo infusion ($p <$ .05; Figures S3, S4, and S5 in Supplement 1), although no subject developed symptoms of hypotension or evidence of cardiovascular insufficiency. No subject developed hypomania during the study. Moreover, the mean YMRS score decreased ($F$ = 9.6; $p >$ .006) between baseline (mean = 2.1 ± .91) and study end (1.2 ± 1.0).

**Table 2.** Side Effects Reported Under Scopolamine and Placebo Conditions Presented as Number of Cases

| Side Effect | Placebo ($n$ = 22) | Drug ($n$ = 22) |
|---|---|---|
| Drowsiness | 13 | 17 |
| Dry Mouth | 3 | 18 |
| Blurred Vision | 4 | 16 |
| Lightheadedness | 4 | 15 |
| Dizziness | 3 | 9 |
| Hypotension (No Intervention) | 0 | 1 |
| Nausea | 0 | 0 |
| Headache | 0 | 1 |
| Nervousness | 1 | 1 |
| Diplopia | 0 | 0 |
| Palpitations | 3 | 0 |
| Derealization | 0 | 0 |
| Mental Clouding | 0 | 0 |
| Irritability | 0 | 0 |
| Restlessness | 0 | 0 |
| Euphoria | 0 | 0 |
| Vertigo | 0 | 1 |

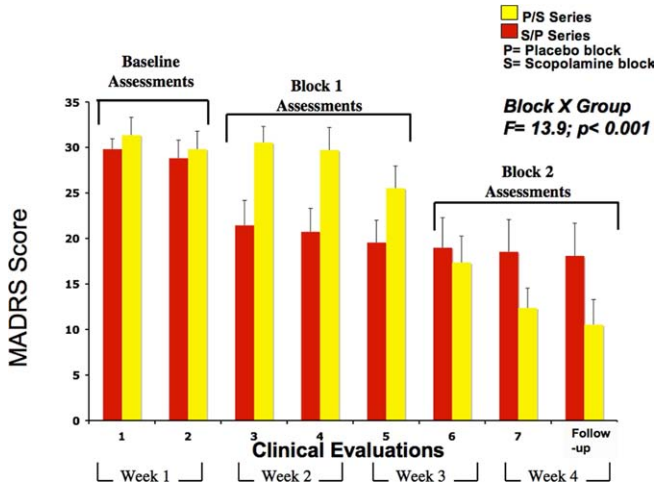


**Figure 2.** Mean Montgomery-Asberg Depression Rating Scale (MADRS) scores for the P/S group (yellow bars) and the S/P group (red bars) across eight assessments. P indicates the placebo sessions and includes a block of three assessments of placebo infusions; S indicates the scopolamine sessions and includes a block of three assessments of scopolamine infusions. Two baseline, three Block 1, and three Block 2 assessments are identified. Error bars show standard error of the mean. The $p$ value reflects a significant block by group interaction.

## Primary Outcome Indexes

The mean MADRS scores for the two groups across the eight evaluations appear in Figure 2. Repeated measures ANOVA showed a group-by-assessment interaction ($F$ = 8.36, $p <$ .001). The three-way ANOVA (group-by-study block-by-assessment) was also significant ($F$ = 14.0, $p <$ .001). For the difference between baseline and study Block 1, the group-by-block interaction was significant ($F$ = 8.32, $p$ = .009). This effect was attributable to the reduction in MADRS scores in the S/P group ($F$ = 22.4, $p$ = .001) being greater than the corresponding reduction in the P/S group ($F$ = 5.18, $p$ = .046, i.e., placebo effect). This difference between groups showed an effect size of 1.38 (Cohen's $d$: confidence interval [CI] = −2.22 to 3.51) and reached significance by the first evaluation in study Block 1 ($t$ = 2.79, $p$ = .011).

Between experimental Blocks 1 and 2 the change in MADRS scores also differed between groups ($F$ = 15.8, $p$ = .001; Cohen's $d$ = 2.27: CI −1.28 to 6.52). This effect was attributable to a reduction in MADRS scores in the P/S group between Blocks 1 and 2 ($F$ = 48.0, $p <$ .001), whereas the MADRS scores in the S/P group did not change in Block 2 versus Block 1 ($F$ = .733; $p$ = .41), indicating that the antidepressant effect observed in this group in Block 1 persisted as they received placebo in Block 2. For the group that received scopolamine second, the difference between the final evaluation in Block 1 and the first evaluation in Block 2 (i.e., the first post-scopolamine assessment) was significant ($t$ = 3.98, $p$ = .003). Within each scopolamine block, the reduction in MADRS scores in the final assessment relative to the first was significant ($t$ = 2.52; $p$ = .020; for S/P and P/S subjects combined) showing further reduction in symptom severity following repeated scopolamine administrations.

By study end, 14 of the 22 (64%) subjects achieved a full response and 11 (50%) experienced remission (based on attaining a MADRS score <10; Table 3). Further post hoc assessments of the antidepressant effects of scopolamine appear in Supplement 1.

**Table 3.** Outcome Indexes For Patients Treated With Scopolamine ($n = 22$)

| | Baseline Block | Block 1 | Block 2 |
|---|---|---|---|
| S/P Group (n = 11) | | | |
| Full response (>50%) | 0 | 4 | 5 |
| Partial response (25–49%) | 2 | 3 | 1 |
| Nonresponse (<25%) | 9 | 4 | 5 |
| P/S Group ($n = 11$) | | | |
| Full response | 0 | 1 | 9 |
| Partial response | 0 | 3 | 1 |
| Nonresponse | 11 | 7 | 1 |

Each entry reflects the number of participants from the identified group showing the described effect. When the two groups were combined, by study end, 14 of the 22 (64%) subjects achieved a full response (11 of whom experienced remission based on attaining a Montgomery-Asberg Depression Rating Scale score ≤ 10). Of these, one subject attained full response and remission under placebo, and this response persisted during the subsequent scopolamine sessions. The remaining subjects achieved full response and/or remission under scopolamine.

P/S, subjects randomized to receive placebo in study Block 1 and scopolamine in Block 2; S/P, subjects randomized to receive scopolamine in Block 1 and placebo in Block 2.

### Secondary Outcome Measures

The CGI-I (from Session 2 through follow-up) showed a group by assessment interaction ($F = 5.49$, $p = .003$), whereas the corresponding interaction for HARS was not significant ($p > .20$). Considering change from baseline, the block-by-group interaction was significant for the CGI-I ($F = 26.3$, $p = .001$; Figure 3B), whereas this interaction for the HARS trended toward significance ($F = 2.6$; $p = .10$; Figure 3A).

The VAS and POMS ratings indicated that no acute, within-session changes in emotion ratings occurred during scopolamine relative to placebo sessions (Supplement 1). Of the VAS ratings, the drug-by-time interaction was not significant for happiness, sadness, anxiety, irritation, restlessness, or alertness ($p > .15$) but was significant for drowsiness ($F = 7.2$; $p = .002$). On the POMS, the drug-by-time interaction was not significant for the depression ($p = .35$), anger ($p = .66$), or tension factors ($p = .32$). However, the drug-by-time interaction on the POMS vigor factor was significant ($F = 7.8$, $p = .003$), because this factor decreased at 20 and 60 min after the start of the scopolamine infusion and then returned to baseline levels by session-end.

## Discussion

Scopolamine (4.0 μg/kg IV) showed antidepressant efficacy relative to placebo in unipolar depressive patients, replicating the results we obtained previously in an independent sample of depressed patients that included both unipolar and bipolar patients (2). Our study used a crossover design, so the improvement observed independently in the two treatment groups provided additional, within-study replications of the antidepressant effect. Between the baseline block and experimental Block 1, the S/P group showed a greater reduction in MADRS scores under scopolamine than under the baseline placebo, and this reduction exceeded that seen concomitantly in the P/S group while they received placebo. In addition, subjects randomized to the P/S schedule showed a reduction in MADRS scores during experimental Block 2 versus Block 1 as they transitioned from placebo to scopolamine.

As in our initial study, the rapidity of the antidepressant response was evidenced by the improvement seen in the evaluation that followed the first scopolamine administration, 3 to 5 days after the first treatment. In both treatment groups, the initial post-scopolamine MADRS ratings were lower than those obtained during the previous session. Moreover, the reduction in MADRS scores seen in the S/P group after their first scopolamine exposure exceeded the corresponding reduction observed in the P/S group under placebo. Each session's assessment evaluated symptoms experienced since the previous visit, so this finding indicated that the antidepressant effects occurred within 3 to 5 days, and treatment responders generally reported improvement in symptoms by the morning following the first infusion. This time frame compares favorably to the 3 to 4 weeks typically required for conventional treatments to become effective.

Other findings from this study that replicated those of our previous study merit comment. First, subjects showed further improvement across the scopolamine block, suggesting that repeated administrations provided additional benefit. Second, in individuals who received scopolamine during Block 1, the improvement seen during drug administration persisted as they received placebo during Block 2, indicating the antidepressant

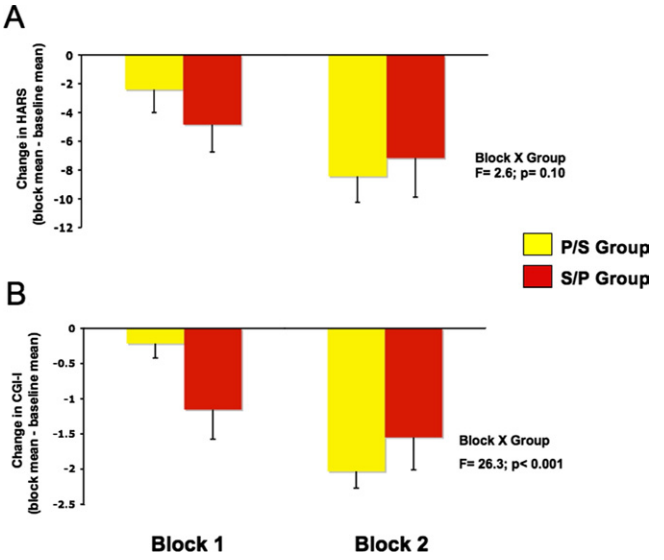


**Figure 3.** Mean changes in **(A)** the Hamilton Anxiety Rating Scale (HARS) and **(B)** the clinical global impressions-improvement scores (CGI-I) between study Block 1 versus the baseline Block (left bar) and between study Block 2 versus baseline (right bar). **(A)** The HARS data showed a nonsignificant trend in the block by group interaction ($F = 2.6$; $p = .10$). To accommodate the variation in mean baseline HARS scores between the S/P and P/S groups ($20 \pm 9$ and $18 \pm 8$, respectively) the effect of scopolamine on anxiety ratings was evaluated within each group separately. In the P/S group, a block-by-assessment analysis indicated differences among study blocks ($F = 10.4$, $p = .005$). Anxiety scores in the P/S group were lower in study Block 2 compared with baseline ($F = 23.0$, $p = .001$), this effect was significant with the first assessment in Block 2 ($t = 2.7$, $p = .022$). The difference between baseline and experimental Block 1 was not significant ($F = 2.6$, $p = .14$). In the S/P group, the block-by-assessment analysis showed a nonsignificant trend toward differing among blocks ($F = 3.8$, $p < .063$). In this group, the HARS scores evaluated in Block 1 were lower than baseline ($F = 7.17$ $p = .023$) and the scores in Block 2 were lower than baseline ($F = 8.03$, $p = .018$) but did not differ from the scores obtained in Block 1 ($F = 1.79$, $p = .21$), indicating the antianxiety effect persisted as this group received placebo in Block 2. **(B)** The CGI-I data showed a block-by-group interaction ($F = 26.3$, $p = .001$). The change in CGI-I scores in the S/P group was greater than the change in the P/S group during Block 1 ($F = 6.61$; $p = .018$). No group difference was observed in ratings from study block two evaluations ($F = 1.54$; $p = .23$) suggesting that the magnitude of clinical improvement did not differ after both groups received scopolamine. P indicates the placebo sessions and includes a block of three assessments of placebo infusions; S indicates the scopolamine sessions and includes a block of three assessments of scopolamine infusions.

effects persisted at least 12 to 16 days after the final scopolamine administration. This carryover effect was confirmed by demonstrating that depression ratings did not differ between the S/P and P/S groups in the final study block, when both groups showed improvement relative to the pretreatment baseline.

The demonstration that an antimuscarinic agent produces potent antidepressant effects extends evidence linking muscarinic receptor function to the pathophysiology of mood disorders (9–18), although the precise mechanism underlying scopolamine's antidepressant action remains unclear. The persistence of scopolamine's antidepressant effect for weeks after its expected clearance from plasma (elimination $t_{1/2}$ = 2–4 hours) suggests a mechanism beyond the direct pharmacologic actions on muscarinic receptors. Moreover, the delay in the onset of the antidepressant response until well after the resolution of anticholinergic side effects appears compatible with an effect on transcription of "late-response" genes or synaptic plasticity, rather than a direct action on muscarinic receptors (19).

One effect scopolamine shares with other somatic antidepressant treatments involves the modulation of *N*-methyl-D-aspartate receptor (NMDAR) function. Blocking muscarinic receptors via scopolamine administration reduces mRNA concentrations for NMDAR types 1 and 2 A in the rat brain in vivo (20) and protects hippocampal neurons from glutamate-mediated neurotoxicity in vitro (21). Chronic administration of antidepressant drugs from various classes and repeated electroconvulsive shock reduce cortical NMDAR function (22–24), and treatments associated with a rapid onset of antidepressant effects either exert direct NMDAR antagonist effects (ketamine) (22,25) or induce NMDR internalization (sleep deprivation) (26,27). Taken together with evidence that abnormal glutamatergic transmission is involved in the pathophysiology of depression, these data suggest the hypothesis that scopolamine's effect on NMDAR function plays a role in its antidepressant action.

Another possible mechanism that merits consideration is scopolamine's paradoxical effect of enhancing parasympathetic autonomic outflow when administered in the low dose range that encompasses the doses used here (28). Reductions in heart rate and BP during scopolamine administration like those we observed (Supplement 1) have been reported previously at comparable doses (29,30) and putatively reflect central effects on autonomic function (28). Although it remains unclear whether the effect of scopolamine (at 4.0 μg/kg IV) on parasympathetic activity plays any role in the antidepressant response, it is noteworthy that the pathophysiology of depression is associated with a reduction in the parasympathetic-to-sympathetic balance (31). The scopolamine effect of enhancing parasympathetic tone may thus reverse this pathologic state, analogous to the effect of some neurostimulation approaches that produce antidepressant effects and also enhance the parasympathetic-to-sympathetic ratio (32).

Patient acceptance of the adverse effects was good; no subject dropped out because of a drug side effect. This favorable tolerability was attributable partly to the transient nature of the side effects and the approximately biweekly, as opposed to daily, dosing schedule. Thus, although scopolamine administration acutely produced sedation, visual blurring, dry mouth, light headedness and dizziness, and small reductions in heart rate and BP (which were clinically nonsignificant in our subjects) these side effects were relatively transient. For example, blurred vision and light-headedness lasted 1 to 2 hours, and sedation typically lasted 2.5 to 3.0 hours, and ranged to as long as 5 hours. Nevertheless, subjects spent the days between infusions without side effects and did not develop adverse reactions commonly associated with daily antimuscarinic administration, such as urinary retention or constipation. Finally, although the POMS data indicated that patients experienced a transient increase in subjective confusion during the 2-hour period following scopolamine infusion, no subject developed delirium, psychosis, or overt confusion, and scopolamine's effects on performance on selective attention were neither generalized nor unidirectional (33). The transient nature of the side effects also aided the preservation of the double-blind because the primary outcome measure (MADRS) was obtained at the beginning of each session when subjects were side-effect free (i.e., before they received the infusion for that day).

Another design feature that mitigated the likelihood of unblinding by side effects was that the placebo challenge, which involved IV infusion while sitting in a reclining hospital chair or bed, commonly produced side effects similar to those expected under scopolamine. For example, 13 of the 22 subjects reported experiencing sedation under placebo. Most of these subjects also spontaneously reported believing that they had received the study drug while actually having received only placebo. In these cases, the experience of subsequently receiving scopolamine may have compromised their blind during Study Arm 2 (i.e., by contrast with previous sessions), but this would not have influenced their ratings obtained during the placebo sessions in Study Arm 1. Moreover, subjects were unaware that the three scopolamine sessions would occur consecutively in a block, reducing the likelihood that experiencing side effects during the previous session would bias the ratings obtained at the beginning of the subsequent session.

The post hoc item-by-item analysis of the MADRS indicated that the reductions in total MADRS scores were attributable to improvements in most symptom domains assessed. There was no evidence of a euphoric effect under scopolamine and the within-session VAS and POMS assessments revealed no acute positive effects of scopolamine on mood (Supplement 1). In contrast, the POMS and VAS scales suggested that subjects showed subtle but statistically significant improvements in mood across the 2.5-hour sessions during the placebo sessions, which did not occur during the scopolamine sessions (Supplement 1).

Fifty-percent ($n$ = 11) of the subjects experienced remission, which occurred under scopolamine in 10 subjects and under placebo in 1. Similarly, in our original study 56% of subjects remitted under scopolamine (2). These results compare favorably to the 10% to 20% placebo-adjusted remission rates obtained using selective serotonin reuptake inhibitors (34).

The effect sizes of the difference between scopolamine and placebo in this study ($d$ = 1.2 and 1.7 for Blocks 1 and 2, respectively) also compare favorably to those typically observed in antidepressant treatment studies, which range from .5 to 1.1 in moderately and severely depressed cases, respectively (35). The subjects studied herein manifested depression severity in the moderate-to-severe range, as reflected by their relatively high mean MADRS scores (Table 3). Although the effect sizes obtained herein were numerically smaller than those seen in our original study, the Cohen's $d$ values nevertheless fell within the confidence intervals of those from our original study. The clinical significance of this antidepressant response was further reflected by the robust change in the mean CGI score (Figure 3).

Several aspects of the sample selection limit the generalizability of these results. First, the sample was small. Second, elderly and pediatric subjects, bipolar depressives, and current nicotine users were excluded, so the current results may not generalize to

such cases. As in our original study, smokers were excluded because we were uncertain whether functional interactions between the muscarinic and nicotinic cholinergic receptor systems might influence the antidepressant effect of scopolamine. Because of sample size limitations, we did not address sex effects on scopolamine's antidepressant efficacy, although such effects have been reported for conventional antidepressant drugs. Finally, although these data are significant and replicate our previous results, they await independent replication.

Our results hold promise that scopolamine treatment offers rapid, robust relief of symptoms to individuals suffering from depression. We previously proposed that the powerful effects we report with scopolamine may have been missed in previous studies using this agent in depressed patients because these studies used lower effective doses (13,15) or assessed clinical effects only acutely (120 min) (36). For example, small but statistically significant antidepressant effects were observed the day following the administration of scopolamine .4 mg administered intramuscularly (13), which would have a bioavailability similar to that of about 2 μg/kg IV (37). Nevertheless the finding that scopolamine at or near the doses we used exerts antidepressant effects awaits replication by an independent laboratory. Finally, determination of the optimal route and schedule of administration for outpatient treatment and the maintenance of scopolamine's antidepressant efficacy during long-term use require further study.

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*The National Institute of Mental Health has filed a use-patent for the use of scopolamine in the treatment of depression, and Drs. Drevets and Furey are identified as coinventors on this pending patent application.*

*ClinicalTrials.gov: The Antidepressant Efficacy of the Anticholinergic Scopolamine: http://www.clinicaltrials.gov/; NCT00369915.*

*Supplementary material cited in this article is available online.*

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