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

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Abstract

Background—We previously reported that intravenous 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, cross-over 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 i.v.)]. Sessions occurred 3-to-5 days apart, such that time spent in each block lasted 1½-2 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 percent reduction in MADRS scores ($p<0.001$) which exceeded the corresponding change of 6.5 percent under placebo (P/S) ($p=0.009$), confirming the *a priori* hypothesis. Improvement was significant at the first evaluation that followed scopolamine administration ($p=0.011$). In block 2 the P/S group showed a 53 percent reduction in MADRS scores ($p=0.001$) following scopolamine versus placebo, while 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 due to side effects.

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

Keywords

antimuscarinic; anticholinergic

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 NIMH showing that the muscarinic cholinergic receptor antagonist,

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scopolamine, exerted antidepressant effects in depressed patients (total n=18) with either major depressive disorder (MDD; n=9) or bipolar disorder (n=9)(2). In this double-blind, placebo-controlled, cross-over trial, subjects underwent multiple sessions in which they received i.v. infusions of placebo or scopolamine (4 μg/kg i.v.). 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 as compared to 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 to 4 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. Since the original sample consisted of both unipolar and bipolar cases, we recognized the need to replicate the findings independently in each mood disorder. The current study thus limited recruitment to MDD subjects.

METHODS

Participants

Volunteers between 18 and 45 years of age evaluated at the NIMH outpatient clinic were assessed for eligibility if they were non-smokers and met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)(3) criteria for recurrent MDD, based upon 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 one year, medical or neurological disorders, narrow angle glaucoma, hypersensitivity to anticholinergic agents, hepatic dysfunction, electrolyte disturbance, HIV or hepatitis viral infection, or weight >125 kg. Pregnant or nursing females also were excluded. Subjects provided written informed consent as approved by the NIMH IRB.

Study Design

During each of seven sessions, subjects received a 15 minute intravenous 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 were obtained prior to infusions, the lead-in placebo in session 1 allowed for a second baseline assessment to be obtained immediately prior to the session 2 infusion. Subsequently, individuals were randomized into either a P/S or S/P double-blind, placebo-controlled, cross-over design whereby P constituted a block of 3 placebo sessions and S a block of 3 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 NIH outpatient pharmacy and assigned by subject number at consenting. Sessions were scheduled 3–5 days apart.

Sample size was determined using power calculations involving data obtained from our initial study, where we observed a group difference in 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 eleven per group provided power of 80 percent for alpha = 0.05.

Assessment

Prior to each infusion, depression severity was rated using the Montgomery-Asberg Depression Rating Scale (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 analog scales (VAS-components included happy, sad, drowsy, irritated, alert, anxious and restless) were administered at baseline and 20, 60, 120 and 150 minutes following initiation of the infusion, and the Profile of Mood State (POMS)(7) was administered at baseline, 20, 60 and 150 minutes post-infusion. 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 Inc., 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 (post-treatment MADRS score≤10) also were 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 versus S/P) by assessments repeated measures 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 the 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 ANOVA's. *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 (see 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 (figure 2). One subject dropped out after randomization but prior to 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 due to non-response; this subject's data were included in the analysis based upon last observation

carried forward. Thus a total of 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 7 infusions the follow-up evaluations could not be obtained for the assessment following session seven (i.e., assessment 8), so analyses were performed using the last observation (from session 7) carried forward (LOCF). The S/P and P/S groups did not differ in MADRS or HARS scores at baseline (F=0.055, p=0.82).

Adverse and Side Effects

Scopolamine was well-tolerated and no medically serious adverse events were encountered. Side effects reported under scopolamine (S) and placebo (P) conditions are listed in table 2. Heart rate, systolic BP and diastolic BP decreased following scopolamine infusion relative to placebo infusion ($p<0.05$; 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; $p>0.006$) between baseline (mean=2.1±0.91) and study end (1.2±1.0).

Primary Outcome Indices

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, $p<0.001$). The 3-way ANOVA (group-by-study block-by-assessment) also was significant (F=14.0, $p<0.001$). For the difference between baseline and study block 1, the group-by-block interaction was significant (F=8.32, p=0.009). This effect was attributable to the reduction in MADRS scores in the S/P group (F=22.4, p=0.001) being greater than the corresponding reduction in the P/S group (F=5.18, p=0.046; i.e., placebo effect). This difference between groups showed an effect size of 1.38 (Cohen's d: CI= −2.22 – 3.51) and reached significance by the first evaluation in study block 1 (t=2.79, p=0.011).

Between experimental blocks 1 and 2 the change in MADRS scores also differed between groups (F=15.8, p=0.001; Cohen's d=2.27: −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, $p<0.001$) while the MADRS scores in the S/P group did not change in block 2 versus block 1 (F=0.733; p=0.41), 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=0.003). Within each scopolamine block, the reduction in MADRS scores in the final assessment relative to the first was significant (t=2.52; p=0.020; 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 11/22 (50%) experienced remission (based upon attaining a MADRS score<10]) (Table 3). Further post-hoc assessments of the antidepressant effects of scopolamine appear in Supplement 1.

Secondary Outcome Measures

The CGI-I (from session 2 through follow-up) showed a group by assessment interaction (F=5.49, p=0.003), while the corresponding interaction for HARS was not significant ($p>0.20$). Considering change from baseline, the block by group interaction was significant for the CGI-I (F= 26.3, P, 0.001; figure 3A), while this interaction for the HARS trended towards significance (F=2.6; p=0.10; figure 3B).

The VAS and POMS ratings indicated that *no acute, within-session changes in emotion ratings occurred during scopolamine* relative to placebo sessions (see Supplement 1). Of the VAS ratings the drug-by-time interaction was not significant for happiness, sadness, anxiety, irritation, restlessness or alertness ($p>0.15$), but was significant for drowsiness ($F=7.2$; $p=0.002$). On the POMS the drug-by-time interaction was not significant for the depression ($p=0.35$), anger ($p=0.66$) or tension factors ($p=0.32$). However, the drug-by-time interaction on the POMS vigor factor was significant ($F=7.8$, $p=0.003$), as 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, i.v.) showed antidepressant efficacy relative to placebo in unipolar depressives, 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 cross-over 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 timeframe compares favorably to the 3 to 4 weeks typically required for conventional treatments to become effective.

Other findings from the current 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 effects persisted at least 12 to 16 days after the final scopolamine administration. This carry-over 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 pre-treatment 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 to 4 hours) suggests a mechanism beyond the direct pharmacological 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 1A and 2A 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 blood pressure during scopolamine administration like those we observed (see Supplement 1) have been reported previously at comparable doses(29, 30) and putatively reflect *central* effects on autonomic function(28). While it remains unclear whether the effect of scopolamine (at 4.0 ug/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 pathological 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, as no subject dropped out due to a drug side-effect. This favorable tolerability was attributable partly to the transient nature of the side effects and the ~bi-weekly, as opposed to daily, dosing schedule. Thus, while scopolamine administration acutely produced sedation, visual blurring, dry mouth, light headedness/dizziness and small reductions in heart rate and blood pressure (which were clinically non-significant in our subjects) these side-effects were relatively transient. For example, blurred vision and light-headedness lasted 1 to 2 hours while sedation typically lasted 2 ½ to 3 hours, and ranged to as long as 5 hours. Nevertheless, subjects spent the days between infusions without side-effect s and did *not* develop adverse reactions commonly associated with *daily* antimuscarinic administration, such as urinary retention or constipation. Finally, while the POMS data indicated that patients experienced a transient increase in subjective confusion during the two 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 since 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 un-blinding by side effects was that the placebo challenge, which involved i.v. 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 to 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 3 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 (see Supplement 1). In contrast, the POMS and VAS scales suggested that subjects showed subtle but statistically significant improvements in mood across the 2 ½ hour sessions *during the placebo sessions* which did not occur during the scopolamine sessions (see Supplement 1).

Fifty-percent (n=11) of the subjects experienced remission, which occurred under scopolamine in 10 subjects and under placebo in one. 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 0.5 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 1). 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. Due to 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, while these data are significant and replicate our previous results, these findings still 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 0.4 mg i.m.(13), which would have a bioavailability similar to that of about 2 ug/kg i.v.(37). Nevertheless the finding that scopolamine at or near the doses we exerts antidepressant effects awaits replication by an independent laboratory. Finally, determination of the optimal route and schedule of administration for out-patient treatment and the maintenance of scopolamine's antidepressant efficacy during long-term use require further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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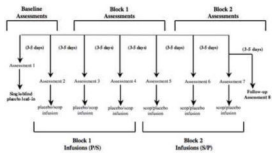

Figure 1.
Study blocked experimental design reflecting infusion series and assessment sessions for each of the two randomized patient groups. P/S reflects the infusion series of placebo followed by scopolamine; S/P indicated scopolamine followed by placebo.

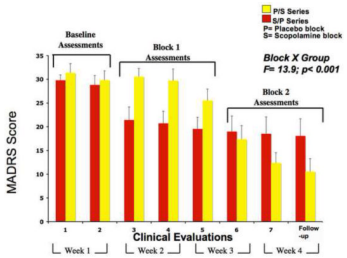

Figure 2.

Mean MADRS scores for the P/S group (yellow bars) and the S/P group (red bars) across eight assessments. P= the placebo sessions and includes a block of 3 assessments of placebo infusions; S= the scopolamine sessions and includes a block of 3 assessments of scopolamine infusions. Two baseline, three block 1 and three block 2 assessments are identified in each panel. Error bars show standard error of the mean. The p-value reflects a significant block by group interaction.

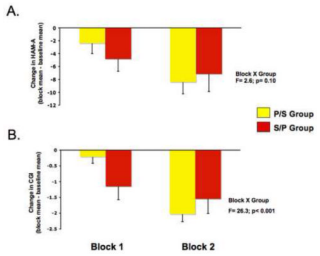

Figure 3.

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=0.10). To accommodate the variation in mean baseline HARS scores between the S/P and P/S groups (20±9 and 18±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=0.005). Anxiety scores in the P/S group were lower in study block 2 as compared to baseline (F=23.0, p=0.001), this effect was significant with the first assessment in block 2 (t=2.7, p=0.022). The difference between baseline and experimental block 1 was not significant (F=2.6, p=0.14). In the S/P group, the block-by-assessment analysis showed a nonsignificant trend toward differing among blocks (F=3.8, p<0.063). In this group the HARS scores evaluated in block 1 were lower than baseline (F=7.17 p=0.023) and the scores in block 2 were lower than baseline (F=8.03, p=0.018) but did not differ from the scores obtained in block 1 (F=1.79, p=0.21), 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, 0.001). The change in CGI scores in the S/P group was greater than the change in the P/S group during block 1 (F=6.61; p=0.018). No group difference was observed in ratings from study block 2 evaluations (F=1.54; p=0.23) suggesting that the magnitude of clinical improvement did not differ after both groups received scopolamine.

Table 1

Patient characteristics at baseline

	Placebo/Scopolamine Group (n=11) (mean ± SD)	Scopolamine/Placebo Group (n=11) (mean ± SD)
Mean age ± SD	30 ± 7.0	33 ± 7.1
Gender	7F/4M	5F/6M
Mean MADRS ± SD	31 ± 6.5	30 ± 3.7
Mean HAM-A ± SD	18 ± 8.2	20 ± 9.2
Chronic illness	8/11	5/11
Comorbid anxiety	3/11	5/11
Unresponsive to treatment	3/11	3/11

In the S/P group (N=11; 5F; 4 African American, 6 Caucasian, 1 Hispanic; mean age=33±7.1 years), 5/11 patients were chronically ill (current episode duration>2 years), 5/11 had a comorbid anxiety disorder and 3/11 were unresponsive to previous treatment. In the P/S group (N= 11; 7F; 4 African American, 6 Caucasian, 1 Hispanic; mean age= 30±7.0), 8/11 patients were chronically ill, 3/11 had a comorbid anxiety disorder, and 3/11 were unresponsive to previous treatment, based upon the response to the most recent therapeutic trial of a conventional antidepressant agent. In total, based upon their history of having either nonresponse to previous treatment, chronicity or a comorbid anxiety disorder(38–41), 16/22 patients had a poor prognosis for response to treatment, including 7 in the S/P group and 9 in the P/S group.

Abbreviations: MADRS – Montgomery-Asberg Depression Rating Scale; HARS – Hamilton Anxiety Rating Scale

Table 2

Side effects reported under scopolamine and placebo conditions presented as number of cases.

Side Effect	Placebo (n of 22)	Drug (n of 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

Table 3

Outcome indices 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
Non-response (< 25%)	9	4	5
P/S group (n=11)			
Full Response	0	1	9
Partial Response	0	3	1
Non-response	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 upon attaining a MADRS 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.

Abbreviations: 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