Brief report

Antidepressant treatment history as a predictor of response to scopolamine: clinical implications

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ARTICLE INFO

ABSTRACT

Background: The intravenous administration of scopolamine produces rapid antidepressant effects. Generally, failing multiple previous antidepressant trials is associated with a poor prognosis for response to future medications. This study evaluated whether treatment history predicts antidepressant response to scopolamine.
Methods: Treatment resistant patients (2 failed medication trials) ($n=31$) and treatment naïve patients (no exposure to psychotropic medication) ($n=31$) with recurrent major depressive or bipolar disorder participated in a double-blind, placebo-controlled, crossover clinical trial. Following a placebo lead-in, participants randomly received P/S or S/P ($P=3$ placebo; $S=3$ scopolamine (4 ug/kg) sessions 3 to 5 days apart). The Montgomery–Asberg Depression Rating Scale (MADRS) was the primary outcome measure. A linear mixed model was used to examine the interaction between clinical response and treatment history, adjusting for baseline MADRS.
Results: Treatment resistant and treatment naïve subjects combined responded significantly to scopolamine compared to placebo ($F=15.06$, $p < 0.001$). Reduction in depressive symptoms was significant by the first post-scopolamine session ($F=42.75$, $p < 0.001$). A treatment history by scopolamine session interaction ($F=3.37$, $p=0.04$) indicated treatment naïve subjects had lower MADRS scores than treatment resistant patients; this was significant after the second scopolamine infusion ($t=2.15$, $p=0.03$).
Limitations: Post-hoc analysis: Also, we used a single regimen to administer scopolamine, and smokers were excluded from the sample, limiting generalizability.
Conclusions: Treatment naïve and treatment resistant patients showed improved clinical symptoms following scopolamine, while those who were treatment naïve showed greater improvement. Scopolamine rapidly reduces symptoms in both treatment history groups, and demonstrates sustained improvement even in treatment resistant patients.

Published by Elsevier B.V.

1. Introduction

Major depression is a severely debilitating illness that affects approximately 14.8 million American adults (Kessler et al., 2005, US Census Bureau, 2013). Approximately 40% of patients with major depressive disorder (MDD) do not respond to the first medication trial (Sackeim, 2001). Response to a conventional antidepressant drug trial is generally not evident for 3 to 4 weeks, and multiple trials are often required to achieve treatment response, which prolongs patient's discomfort and increases the risk of self-harm and harm to others (Insel and Wang, 2009). Given

the need for quicker and more effective therapeutic agents, the identification of novel antidepressants that produce more rapid therapeutic effects and their predictors of response remain critical.

As a novel antidepressant, scopolamine has been shown to produce rapid and robust antidepressant effects in currently depressed unipolar (MDD) and bipolar (BD) patients (Furey and Drevets, 2006, Drevets and Furey, 2010). Scopolamine blocks cholinergic muscarinic receptors, and previous studies have shown cholinergic–muscarinic dysregulation in mood disorders (Janowsky and Overstreet, 1990). While the rate of clinical response has been relatively high (Furey and Drevets, 2006), not all patients respond to scopolamine.

The current study assessed history of treatment response as a potential predictor of response to scopolamine. Previous studies indicate that failing multiple antidepressant trials is associated with a poorer prognosis for future trials (Rush et al., 2006). For

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example, in the STAR*D study, third-step treatments following two traditional antidepressant trials showed modest response rates, suggesting an increased risk of failure after each subsequent failed medication trial (McGrath et al., 2006, Nierenberg et al., 2006). These findings indicate the identification of antidepressants that significantly reduce symptom severity in treatment resistant patients which is vital to the treatment of depression. Clinical practice would also benefit from the identification of first-line antidepressants for treatment resistant depression which would significantly reduce the need for future trials.

The present analysis examined whether treatment history predicts antidepressant response to scopolamine. We hypothesized that subjects would show a significant reduction in depressive symptoms regardless of treatment history.

2. Methods

2.1. Participants

75 subjects (18–55 years of age) with Major Depressive Disorder or Bipolar Disorder were identified for inclusion in this post-hoc analysis. All recruitment and study procedures occurred at the National Institute of Mental Health, and all participants were screened in the inpatient or outpatient clinic. Eligibility was based on meeting criteria for Major Depressive Disorder or Bipolar Disorder as determined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000). All participants were medication free for at least 2 weeks, denied current nicotine use, did not have a history of substance abuse within 5 years, or lifetime history of substance dependence, and were in a current major depressive episode without psychotic features.

Treatment history was characterized through clinician interviews which assessed medical and psychiatric history, including response to each prior medication trial. A failed medication trial was defined as a lack of therapeutic response (lifetime) after adequate duration and dosage (Fava and Davidson, 1996). Of the 75 subjects, 13 were excluded from analysis due to having a history of only one medication trial ($n=7$), or having a partial response to one or more previous medications ($n=6$). The remaining 62 subjects (MDD=49, BP I=1, BP II=12; mean age=32.4, SD=9.5) were categorized as treatment naïve if they never received medication for depression ($n=31$; MDD=27, BP II=4), or as treatment resistant if they failed two or more medication trials of adequate duration ($n=31$; MDD=22, BP I=1, BP II=8). Data for 52 of the original 75 patients have been reported in previous publications (Furey and Drevets, 2006, Drevets and Furey, 2010, Furey et al., 2010).

The study was approved by the Combined Neuroscience Institutional Review Board (IRB) of the National Institutes of Health (NIH). All subjects provided written informed consent before entry into the study.

2.2. Study design

All subjects participated in a double-blind, placebo-controlled, crossover clinical trial consisting of 7 infusion sessions and a follow up evaluation. Each session included clinician administered depression rating scales, followed by a 15 min intravenous infusion of either placebo or scopolamine (4 ug/kg). Following a placebo lead-in, participants were randomly assigned to P/S or S/P where P represents a block of 3 consecutive placebo infusion sessions, and S represents a block of 3 consecutive scopolamine infusion sessions. Each infusion was conducted 3 to 5 days apart, and a follow up evaluation was conducted approximately 3 to 5 days

after the final infusion. During each session, participants completed self-report ratings, as well as clinician administered scales that included the Montgomery–Asberg Depression Rating Scale (MADRS) (Khan et al., 2002) as the primary outcome measure. In cases where follow-up assessments could not be obtained after session 7, or after the final scopolamine infusion ($n=4$), response rate analyses were performed using the last observation carried forward (LOCF).

2.3. Statistical analysis

Baseline MADRS was defined as the average of sessions 1 and 2 for all subjects as both ratings occurred prior to receiving drug. Baseline scores were included as a covariate in the primary analyses.

A treatment group (P or S) by session by treatment history (naïve vs. resistant) factorial linear mixed model was performed on symptom severity (i.e., MADRS). Due to the crossover block design and the potential for carryover effects of receiving drug before placebo, only sessions 3 through 5 were used for drug comparisons. A first order autoregressive covariance structure with restricted maximum likelihood estimation was used. Post-hoc, Bonferroni-adjusted simple effects tests were used to characterize significant interactions identified in the overall model. Significance was defined as $p < 0.05$, two-tailed.

Given the potential for seeing a non-significant drug by treatment history interaction in the initial statistical model based on limited power, a treatment history by session linear mixed model was performed using only the scopolamine phases to determine whether treatment history influences the magnitude of clinical response to scopolamine specifically. A separate model included baseline as a time-point instead of as a covariate to examine changes from baseline to the first assessment post-scopolamine.

Patients were characterized as achieving (1) a full response ($\geq 50\%$ reduction in MADRS scores from baseline), (2) a partial response ($< 50\%$ but $\geq 25\%$ reduction), or (3) no response ($< 25\%$ reduction), as well as achieving remission (MADRS score ≤ 10) by study end in addition to post-scopolamine treatment (Nierenberg and DeCecco, 2001). Chi-square tests were used to compare response and remission rates between treatment history groups.

3. Results

Demographic characteristics of the treatment history groups as well as their baseline depression severity scores (i.e., MADRS) are shown in Table 1. The treatment history groups did not differ on age ($p=0.43$), gender ($p=0.50$), baseline MADRS ($p=0.26$), or duration of illness ($p=0.68$), indicating these factors were reasonably balanced across groups.

Consistent with previous findings (Furey and Drevets, 2006, Drevets and Furey, 2010), we found that patients responded significantly better to scopolamine compared to placebo (drug main effect, $F=15.06$, $df=64.66$, $p < 0.001$). There was a non-significant interaction between drug and treatment history ($F=0.80$, $df=1.65$, $p=0.37$), suggesting both treatment naïve and treatment resistant subjects have a similar response to scopolamine relative to placebo.

Examining scopolamine alone with all available data, a significant session by treatment history interaction ($F=3.37$, $df=2,117$, $p=0.04$) indicated that treatment naïve subjects had lower MADRS scores over time than those who were treatment resistant; this was significant at the second post-scopolamine session ($t=2.15$, $df=104$, $p=0.03$). The reduction in symptoms after the first scopolamine infusion was evident in both treatment groups, and the magnitude of response did not differ between groups at this time point ($t=0.03$, $df=105$, $p=0.98$). Between the