Antidepressant Effects of the Muscarinic Cholinergic Receptor Antagonist Scopolamine: a Review

Supplemental Information

Timing of Onset of Scopolamine's Antidepressant Effects

Although we established that the onset of scopolamine's antidepressant action was evident by 3 days after administration using systematically applied clinical ratings, we did not obtain ratings on the days between the initial infusion session (day 0) and the first follow-up evaluation on day 3 to 5. Nevertheless, participants who reported a change in their clinical status at this first follow-up session routinely were asked when their depressive symptoms had changed. Those participants who observed an improvement in their depression severity generally reported that they experienced relief from their depressive symptoms on the first morning after scopolamine infusion (i.e., within 24 hours of drug exposure). Some subjects additionally reported experiencing a more subtle improvement in depressive symptoms on the first evening and better sleep on the first night that followed the initial scopolamine exposure. These anecdotal descriptions of the course of improvement suggest the antidepressant effect may be evident at 24 hours following exposure.

In contrast, no improvement in mood was evident within 150 min of scopolamine infusion based upon the ratings obtained using the Profile of Mood States (POMS), which was sensitive to acute, within-session change in emotion ratings. 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). There was no evidence of a euphoric effect under scopolamine and the within-session assessments revealed no acute positive effects of scopolamine on mood. In contrast, the POMS data suggested that subjects showed subtle but statistically significant improvements in mood across the 150 min sessions during the placebo sessions which did not occur during the scopolamine sessions (1). Further studies thus are needed to evaluate the antidepressant

efficacy at time-points earlier than day 3 in order to characterize more precisely the timing of the onset of scopolamine's antidepressant effect.

Preliminary Observations Using Scopolamine in Treatment Resistant Depression

The study samples described within the paper consisted of participants who were heterogeneous with respect to their history of responsiveness to conventional antidepressant treatments. Some participants reported having experienced satisfactory clinical improvement in response to previous trials of antidepressant pharmacotherapy, while others reported being non-responsive to previous treatments or were treatment-naïve. Of the subjects studied in these trials, 12 had not responded to an adequate therapeutic trial of a selective serotonin reuptake inhibitor (SSRI) prior to receiving scopolamine based upon self-report or medical record review, and using conventional criteria for establishing the adequacy of a treatment trial via the dose and duration of exposure to specific agents (2). Nine of these 12 subjects (75%) showed a full response to scopolamine (>50% reduction in Montgomery-Asberg Depression Rating Scale scores), similar to the 70% response rate seen in depressed subjects who previously had proven responsive to SSRI agents. Moreover, 11 subjects had failed to respond to adequate therapeutic trials of agents from at least two antidepressant drug classes (some of whom were included in the SSRI-nonresponsive group). Eight of these 11 (73%) showed a full response to scopolamine.

These preliminary data suggest that previous non-response to SSRI may not predict non-response to scopolamine. Although such a conclusion awaits confirmation in a larger sample size of treatment-resistant subjects, these observations are compatible with pharmacological and gene expression data indicating that the therapeutic mechanism of scopolamine differs from that of SSRIs.

Supplemental References

1. Drevets WC, Furey ML (2009): Replication of scopolamine's antidepressant efficacy in major depressive disorder: a randomized, placebo-controlled clinical trial. *Biol Psychiatry*. 67:432-438.
2. Berlim MT, Turecki G (2007): Definition, assessment, and staging of treatment-resistant refractory major depression: a review of current concepts and methods. *Can J Psychiatry*. 52:46-54.