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INVITED COMMENTARY

Serendipity Strikes Again: Scopolamine as an Antidepressant Agent in Bipolar Depressed Patients

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Abstract The adrenergic-cholinergic balance hypothesis of mania and depression suggests that depression may be due to an over-activity or a hypersensitivity to central acetylcholine. From this hypothesis, it is logical that scopolamine, a centrally acting antimuscarinic agent, would be useful as an antidepressant. Authors, working at the Intramural Program at NIMH in Bethesda Maryland have shown that intravenous scopolamine is a rapidly acting, effective antidepressant and have than replicated this finding. They now report that this antidepressant effect occurs in bipolar, as well as unipolar depressed patients. The clinical and theoretical implications of this findng for difficult to treat bipolar depressed patients is considerable, and the finding is in need of independent replication.

Keywords Scopolamine · Depression · Bipolar disorder · Antidepressant · Adrenergic-cholinergic balance hypothesis

The adrenergic–cholinergic balance hypothesis of affective disorders, first proposed by my colleagues and I in 1972 [1], suggests that depression is a disorder of low adrenergic (ie, dopaminergic, noradrenergic) activity relative to central acetylcholine, whereas mania is the converse. At the time that the hypothesis was first published, the primary evidence for the hypothesis was that cholinesterase inhibitors, which increase central muscarinic cholinergic tone, were found to mimic the behavioral manifestations of depression and to rapidly turn off mania [1]. As time went on, genetic, sleep physiology, neuroendocrine, neuroimaging, and animal studies provided information that largely supported the above hypothesis. Following this hypothesis, a logical treatment of depression would be to give depressed individuals the antimuscarinic agent scopolamine and/or other centrally acting antimuscarinic agents. Although several investigators attempted to test the antidepressant properties of a few anticholinergic agents, including scopolamine, the results obtained were equivocal, probably due in large part to dosages being too low.

To date, only one group, the Mood and Anxieties Disorder Program at the Intramural Program of the National Institute of Mental Health (NIMH) in Bethesda, MD, has published and presented controlled studies demonstrating that scopolamine has clear antidepressant properties, and that discovery was essentially made by serendipity. Thus, in 2006, Furey and Drevets [2], studying the cognitive effects of scopolamine in depressed patients, unexpectedly noticed that scopolamine alleviated depression in depressed individuals. In a placebo controlled dose ranging pilot study and later in a controlled study, they noted that intravenous scopolamine hydrobromide, 4.0 μg/kg, rapidly alleviated depression in a mixed group of bipolar depressed and unipolar depressed patients, a phenomenon not noted with placebo or with lower doses of scopolamine [2]. The methodology of the controlled part of their study utilized a double-blind, placebo-controlled crossover trial of scopolamine as described in their 2006 *Archives of General Psychiatry* article [2]. Montgomery-Asberg Depression Rating Scale (MADRS) and the Hamilton Anxiety Rating Scales were applied across sessions. A single-blind, placebo lead-in session was used, followed by individuals being

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randomly assigned to a placebo/scopolamine or a scopolamine/placebo double-blind, placebo-controlled crossover protocol. Each subject received 3 infusions of intravenous scopolamine, followed by 3 infusions of place, each infusion given every 3 to 5 days, or vice versa. Subsequently, these authors and collaborators replicated their work in a new group of patients with only major depressive disorder [3], and in a subgroup analysis, they noted that women were more sensitive than men to the antidepressant effects of scopolamine [4].

Most recently, Frankel and colleagues [5], members of the same Mood and Anxieties Disorder Program at the NIMH, subdivided the patients who had been studied in the controlled trials into those with major depressive disorder (non-bipolar) and those with bipolar depression. The study's purpose was to test the effectiveness of scopolamine specifically in bipolar patients and to compare its effectiveness with that in unipolar depressed patients. The study was reported as a poster at the 9th International Conference on Bipolar Disorder, held in Pittsburgh, PA, in June 2011 [5].

Using data derived from the studies described above [2–4], Frankel and colleagues [5] studied 14 patients with bipolar depression and compared these with 38 patients with non-bipolar major depressive disorder. They found that for the patients with bipolar disorder, changes in MADRS scores indicated that scopolamine was significantly and dramatically more effective in lowering depression scores than placebo ($P<0.001$). As with the previous studies, overall, the effect was shown by the first post-drug assessment and did not differ significantly from that shown in the non-bipolar major depressive disorder patients. Hamilton Anxiety scores were also lower during the active drug phases than during placebo phases. Significantly, the Young Mania Rating Scale scores did not change when scopolamine was compared with placebo, suggesting no activation of mania in the 14 individuals studied.

This set of studies illustrates several important issues. Scopolamine exhibited a strong antidepressant effect that was rapid in onset. Especially notable is that this effect occurred in bipolar patients, given the recent literature showing that antidepressant treatment of bipolar depression may not be as effective as previously thought or hoped for, and that such treatment may actually be destructive. If equivalent doses of scopolamine exist in an oral form, and if such treatment proves effective, an inexpensive and novel way of treating bipolar depression may have been discovered (ie, a "new old way"). Using the intravenous route would be cumbersome but possible as well. Routes such as intranasally or transdermally administered scopolamine may also prove useful and should be explored.

The study is especially important given the treatment-resistant nature of bipolar depression. One could envision beginning scopolamine treatment early in the course of treatment of a bipolar depression, and then later or simultaneously adding in a selective serotonin reuptake inhibitor or serotonin–norepinephrine reuptake inhibitor, or a tricyclic antidepressant or mood stabilizer.

However, only one group, the Mood and Anxieties Disorder Program at the NIMH, has demonstrated clear efficacy for scopolamine. It is very encouraging that this group has replicated itself once, and that the original controlled study followed an unexpected observation, thus suggesting that the authors did not have an initial theoretical or economic bias as to expected results until they saw them appear.

Nevertheless, this work is in great need of independent replication by another group of researchers to establish full credibility. To this point, it is significant that no such study has occurred to date, although the original work was published in the *Archives of General Psychiatry* in 2006. This contrasts the effects of ketamine on depression, published around the same time, which have been subsequently studied extensively. This difference may speak to the role of novelty and fad and/or commercial potential in directing our scientific endeavors, or possibly just differences in researchers' scientific interests.

Like so many of the most important findings in psychopharmacology, this finding initially was made by a combination of keen observation, open minds, and serendipity, and cost to start with only what the relatively unrelated work cost. It was neither based on a theory nor the logical consequence of well-supported scientific thinking as such, although such thinking did exist. It is probably not by chance that this discovery occurred at the NIMH Intramural Program, a place in which science is not so tightly reviewed or controlled, and where relative freedom to explore promising leads exists. The NIMH Intramural Program, although subject to review, is not a place in which rigid peer review and "promising early results" determine funding, and one must adhere tightly to what he or she said he or she would do, such as occurs in the extramural world. It is also not by chance that the main work on ketamine, another novel antidepressant reported at the same time scopolamine was, also occurred under the auspices of the NIMH Intramural Program.

The scopolamine studies add considerable support to the adrenergic–cholinergic balance hypothesis of mania and depression [1]. It is a proof-of-concept study that has previously been missing from the literature. Most support for this hypothesis, until the scopolamine studies were published, has come from the observed effects of muscarinic agonists and cholinesterase inhibitors, such as physostig-

mine, arecoline, and related compounds. These have been found to cause depression and its biological manifestations, such as increased serum adrenocorticotropic hormone and β endorphin, increased rapid eye movement (REM) sleep and decreased REM latency, super-shortening of REM latency in depressed patients, and induction of depression and the above REM changes in unaffected close relatives of depressed patients. Similar effects have been found in animal models.

Thus, it will be interesting to see what happens next, and whether this intriguing and potentially important therapeutic and theoretical finding holds up and leads to a plethora of new drug treatments, or whether, like so many promising treatments before, it passes into the sands of history.

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