Naltrexone and Scopolamine Rapidly Reduce Symptoms of Major Depressive Disorder (MDD): A Double-Blinded Randomized Controlled Pilot Study.

Original Research

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Abstract

Background: Scopolamine and naltrexone are FDA-approved medications that have been utilized off-label for the indication of major depressive disorder (MDD). We examined the efficacy of the two medications in combination for major depression.

Methods: Fourteen adults (seven female and seven males) with current major depressive disorder were randomized to 0.15 mg twice daily of scopolamine and 1 mg twice daily naltrexone or placebo for a total of 4 weeks. Montgomery–Asberg Depression Rating Scale (MDRS) questionnaires were utilized to monitor progress in depression symptomatology. The placebo patients were crossed over to the active medications subsequent to the four-week trial period.

Results: Two subjects dropped out of the trial as a result of side effects. A total of 12 subjects completed the trial. The average reduction in MDRS scores over the four weeks for the active medications was 12.5. The average reduction noted in control patients was 3.5. This difference was statistically significant with P = 0.03, less than 0.05 for a greater than 95% confidence interval. Of the 4 patients who crossed over to the active medications, three additional patients noted a partial or complete response to the medications with an average reduction and MDRS scores of 8.

Limitations: Small sample group.

Conclusion: The combination of scopolamine and naltrexone demonstrated significant benefit for MDD. A larger study is currently underway.

Introduction:

Depression is currently a silent pandemic, and, according to the World Health Organization, accounts for more disability worldwide than any other medical problem. Most individuals with depression do not receive treatment. Those that do are treated with many modalities with only fair efficacy. More than a third of treated patients do not achieve remission with current treatments. A number of recent studies have utilized antidepressant medications in combination. Generally, synergy is noted with increased levels of response and remission reported, often with no increased adverse-effect burden.

Naltrexone is an opioid antagonist, FDA-approved for treatment of ethanol use disorder as well as for opioid use disorder. Naltrexone Hydrochloride is a competitive opioid antagonist at both mu and delta opioid receptors. An oral dose of 50-100 mg can reverse opioid overdoses. Paradoxically, ultra-low dose naltrexone (less than 1 mcg) enhances the effects of opioid agonists. Naltrexone binds to the C-terminal pentapeptide of the scaffolding protein filamin A with strong avidity which may prevent or reverse a change in G-protein signaling in G-coupled receptor systems, such as the mu opioid receptor after prolonged stimulation by an agonist. Low dose naltrexone has additionally been anecdotally found to be helpful in many disorders, including fibromyalgia, which has symptom overlap with depression. Naltrexone has recently been noted in a pilot study to be effective in treating depression relapse in patients utilizing dopaminergic antidepressants.[1]

Scopolamine has been demonstrated to be a rapid acting antidepressant administered both as an IV infusion as well as dosed orally. Interest in the muscarinic cholinergic system in mood disorders stemmed initially from evidence suggesting hypersensitivity of the cholinergic system plays a role in the pathophysiology of depression. Researchers have shown increasing cholinergic activity exacerbates depressive symptoms. Two studies have demonstrated that scopolamine administered both IV and orally result in rapid remission from major depression in a majority of patients.[2-4] The principle investigator has utilized scopolamine in the treatment of depression and anxiety IV and orally with a high level of efficacy and minimal side effects.

We carried a study utilizing the oral route of administration in order to maximize convenience and cost effectiveness. The 1mg B.I.D. (twice daily) naltrexone dose and 0.15 mg B.I.D. dose of scopolamine combination was chosen based on our clinical experience with the medications, and our desire to maximize both efficacy and tolerability.

Methods:

The study was approved by Integreview IRB, informed consent was obtained, and the study was registered at Clinicaltrials.gov: #NCT03386448. Charlotte North Carolina area men and women with MDD were recruited by Internet and billboard advertisement.

Inclusion criteria included: Age 18-65; written informed consent; meeting clinical diagnosis of ma-

jor depressive disorder (MDD) through interview and also through Montgomery–Asberg Depression Rating Scale (MDRS) score greater than or equal to 20. All subjects had previously utilized at least one other antidepressant medication. Accepted subjects had no changes in current medications for the last four weeks.

Exclusion criteria included: suicidal ideation; severe kidney or liver disease; recent change in medication; allergy or hypersensitivity to naltrexone or scopolamine; use of opioids or MAO inhibitors; glaucoma; schizophrenia; pregnancy or lactation.

The patients were randomized into an active medication group and a control group (seven patients each group). The patients began the medication and were reevaluated weekly. At the four-week point, the medication codes were identified. All control medication patients elected to begin active medication, and five out of the six in the active group continued the active medications. In the active group, bupropion was added to the regimen of three patients with no response or only partial responses, and the medication doses were increased to a maximum of 0.5 mg of scopolamine and 3mg daily of naltrexone in non-responders.

Subsequently, three patients from the control group noted at least a partial response with the active medications. In the active group, of the two patients who did not initially respond, no significant improvement was noted later.

Results:

Two subjects dropped out of the trial as a result of side effects. A total of 12 subjects completed the trial. The average reduction in MDRS scores over the 4 weeks for the active medications was 12.5. The average reduction noted in control patients was 3.5. This difference was statistically significant with P = 0.03, less than 0.05 for a greater than 95% confidence interval. Of the four patients who crossed over to the active medications, three additional patients noted a partial or complete response to the medications with an average MDRS score reduction of eight.

Discussion:

Depression is currently a silent pandemic, and according to the World Health Organization accounts for more disability worldwide than any other medical problem. Most individuals with depression do not receive treatment. Those that do are treated with many modalities with only fair efficacy. More than a third of treated patients do not achieve remission with current treatments.

Scopolamine has been demonstrated to be a rapid acting antidepressant administered both as an IV infusion as well as dosed orally. Naltrexone has recently been noted in a pilot study to be effective in treating depression relapse in patients utilizing dopaminergic antidepressants.[1] In this pilot study, we demonstrated a rapid and robust improvement in depression symptoms with the combination of scopolamine and naltrexone. Side effects were generally minimal, though two subjects did drop out of the study.

Conclusion:

This pilot study demonstrated a robust and rapid reduction in a majority of depressed subjects with a tolerable side-effect profile. This combination has significant potential as an adjunct treatment for treatment-resistant MDD or potentially as a first-line treatment. A larger open trial is underway evaluating the efficacy of scopolamine as a monotherapy for MDD.

References:

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