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EXPERT REVIEWS

Oral scopolamine augmentation for major depression

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Changsu Han[1] and Chi-Un Pae*[2,3]

[1]*Department of Psychiatry, Ansan Hospital, Korea University, College of Medicine, Ansan, Kyeonggi-Do, South Korea*
[2]*Department of Psychiatry, Bucheon St. Mary's Hospital, The Catholic University of Korea College of Medicine, 2 Sosa-Dong, Wonmi-Gu, Pucheon, Kyounggi-Do 420-717, South Korea*
[3]*Department of Psychiatry and Behavioral Medicines, Duke University Medical Center, Durham, 2218 Elder Street, Durham, NC 27705, USA*
**Author for correspondence: pae@catholic.ac.kr*

Evaluation of: Khajavi D, Farokhnia M, Modabbernia A *et al.* Oral scopolamine augmentation in moderate to severe major depressive disorder: a randomized, double-blind, placebo-controlled study. *J. Clin. Psychiatry* 73(11), 1428–1433 (2012).

Major depressive disorder (MDD) is a chronic, recurrent and devastating mental illness affecting approximately 16% of individuals in the USA in their lifetime. Selective serotonin reuptake inhibitors are the most widely prescribed and standard antidepressants in the treatment of MDD. The reason for such antidepressants being the first-trial antidepressant treatment choice has mainly come from proven efficacy, florid experience, and improved tolerability and safety compared with older antidepressants. However, currently available evidence from placebo-controlled or large practical clinical trials have demonstrated that the efficacy of such modern antidepressants is still limited to MDD patients in full remission as well as functional recovery in clinical practice. Almost 70% of MDD patients fail to remit after initial antidepressant treatment, and the risks to relapse and recurrence dramatically increase with further treatment steps. Thus, clinicians conclude that they have to make a proper and timely decision in management of their MDD patients in clinical practice, depicting that better understanding regarding diverse treatment strategies are not optional but mandatory for difficult-to-treat patients with MDD. Among different treatment strategies, augmentation with current antidepressant is attractive since it does not need any delay in switching to a different antidepressants, prevents loss of efficacy from previous antidepressants, enhances the efficacy of initial antidepressants or produces a synergistic effect with current antidepressants. Recently, Khajavi *et al.* investigated the efficacy and safety of oral scopolamine (anticholinergic agent) augmentation in moderate-to-severe MDD in a randomized, double-blind, placebo-controlled clinical trial (randomized controlled trial). This article summarizes the study background, methods and important results. Clinical implications, related practical issues, major pitfalls and future research direction are also presented.

Keywords: antidepressant • augmentation • depression • scopolamine

Augmentation of diverse psychotropics to antidepressants is commonly recommended as the second approach when patients with major depressive disorder (MDD) do not adequately respond to initial antidepressants after an appropriate antidepressant trial [1]. Recently, new augmentation agents such as creatine have been tried, and it has been found that these may be effective and tolerable in the treatment of MDD [2].

Available evidence proposes that central cholinergic pathways are involved in the regulation of mood and cognition. In fact, many animal and human studies suggested that alteration of cholinergic activity in the brain is potentially related to the development of depressive symptoms and is also associated with antidepressant effects [3].

Recently, Khajavi *et al.* investigated the efficacy and safety of oral scopolamine (an anticholinergic agent) augmentation in moderate-to-severe MDD in a randomized, double-blind, placebo-controlled clinical trial [4]. This article discuses the clinical significance, related practical issues, potential limitations and future research implications based on the findings of the original study.

Summary of methods & results

Participants were all outpatients with moderate-to-severe MDD recruited from two hospitals.

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Inclusion criteria were age 18–55 years, diagnosis of MDD (based on DSM-IV_TR criteria) and 17-Item Hamilton Depression Rating Scale (HAMD-17) score ≥22 and a score of ≥2 on item 1 of the HAMD-17.

Forty patients were enrolled in the study and none discontinued early; 20 patients were randomly assigned to the scopolamine hydrobromide (containing 0.5 mg active ingredient) plus citalopram group (SPCG) and another 20 patients were assigned to the placebo plus citalopram group (PBCG) for 6 weeks. The dosage of citalopram was 20 mg/day for the first week and then 40 mg/day for the subsequent 5 weeks. The primary outcome measure was HAMD-17 total score change from baseline to that recorded in week 6 in the SPCG versus the PBCG. Early improvement (≥20% reduction in the HAMD-17 total score at the end of the first and second weeks), response rates (≥50% reduction in the HAMD-17 total score from the baseline to week 4 and 6) and remission rates (HAMD-17 total score ≤7) at the end of the trial were also compared between the two groups. Adverse events (AEs) were systematically collected using a checklist at each visit.

The baseline HAMD-17 total scores were not different between SPCG and PBCG (24.5 vs 24.2, respectively). At the end point, an approximately 74% reduction in the HAMD-17 score was seen in the SPCG, while 59% of reduction was noted in the PBCG, where the magnitude of difference between the two groups significantly favored the PBCG, even after controlling the baseline score ($F = 12.518$; $p = 0.001$). An effect size of 0.9 was observed for the difference in HAMD-17 score reduction between the two groups at the end point. In addition, these differences were evident at day 4, week 4 and week 6. In addition, the early improvers were also significantly higher in SPCG than in PBCG (70 vs 35%, respectively). Response rates were higher with SPCG than PBCG at week 4 (65 vs 30%), but not at week 6. Remission rates of SPCG were also higher than PBCG at week 6 (65 vs 20%). Dry mouth, dizziness, drowsiness and blurred vision were noted in at least 35% in the SPCG, while in the PBCG these were found in 15–25%.

Discussion

The study by Khajavi *et al*. tested for the first time the oral formulation of scopolamine (preferable route of administration for routine clinical practice) in contrast to the previous trials (all of which used scopolamine injection) [4]. Citalopram was selected as the initial antidepressant at baseline in the study, which is a sufficiently representative, acceptable (e.g., benefit/risk/cost) and widely prescribed antidepressant worldwide, indicating that the study was designed for resemblance of natural treatment setting. The anticholinergic activity of paroxetine was found to be moderate compared with other antidepressants [5]. Therefore, scopolamine augmentation with paroxetine should be carefully monitored for possible potentiation of anticholinegic AEs, especially in older patients with MDD. Polypharmacy is very common and psychotropics are the second common polypharmacy agents leading to idiosyncratic adverse reactions [6]. The effect of antidepressants on cognitive functions is easily impaired by muscarinic antagonists such as scopolamine. In particular, older antidepressants showed significant memory impairment, and also potentiated scopolamine-induced memory deficit in a significant way. However, fluoxetine significantly reversed the scopolamine-induced cognitive defects. Hence, bidirectional influences on cognitive functions between antidepressants and scopolamine warrant more research [7].

Another favorable aspect of this study was not to include highly recurrent and chronic patient populations who are not very complicated by previous treatment failures. Thus, the augmentation effect of scopolamine may not be significantly compromised by such critical clinical factors.

According to the results from the study of Khajavi *et al*., the remission rates of 65% were robust compared with previous clinical trials that investigated the augmentation effects of certain medications [1,8]. For instance, the remission rates from aripiprazole and quetiapine augmentation ranged from 26 to 37%, respectively, indicating the remitters were significantly higher with scopolamine augmentation than with atypical antipsychotic augmentation in patients with MDD, although the study sample characteristics were quite different among such trials. In addition, the remission rate was also higher than those from acute (37.7–38.9%) and chronic (41.8–46.6%) treatment phases of the CO-MED trial that investigated the effect of different antidepressant combination therapies in a naturalistic treatment setting. However, no conclusive remarks can be made until we have direct comparison studies between these augmentation and combination treatments in patients with MDD.

The rapid onset of scopolamine augmentation was seen from day 4 after commencement of the drug, which is in line with a previous quetiapine augmentation study [8]. In addition, the improvement by week 4 (-13.2) accounted for 73.7% of total improvement (-14.8) at the end point during the study, while an additional 26.3% improvement was also noted thereafter during the study. This finding is consistent with previous studies, indicating that most improvement with augmentation therapy may be achieved within 2–4 weeks of such treatment [1,8]. These findings may deliver a clinical wisdom for clinicians early in decision-making when the patient fails to show the expected response from current treatment. In fact, nonresponse as early as week 2 was found to be associated with prediction of poor treatment outcome [9].

The limitations of this study are also clear. A structured assessment for diagnosis of MDD was not used, pointing to a potential assessment bias. The study could not inform clinicians of the scopolamine dose, since they did not use differential fixed dose design during the study. Future studies will need a more informative and practical design in the dose titration of scopolamine. The study also did not include comorbid psychiatric and medical disorders, indicating a limited generalization, as complicated patients are more prevalent in clinical practice, as seen in the STAR*D trial, and also require further treatment steps due to the nature of treatment resistance [10]. The sample size was also too small to translate the results into clinical practice.

Expert commentary & five-year view

There has been some progress in trials of unique augmentation agents based on their pharmacological profile. Creatine monohydrate augmentation with selective serotonin reuptake inhibitor treatment was also found to be a promising agent, showing more

rapid and efficacious responses in women with MDD [2]. Creatine is not designed for treating MDD but has involvement in enhancing the phosphocreatine energy pool, leading to improvement of cellular bioenergetics associated with symptoms of MDD [2]. These therapeutic approaches with various augmentation agents may provide clinicians with more viable treatment options in the treatment of MDD.

Despite the profound efficacy of scopolamine observed in the study, the AE profile of scopolamine should be a crucial barrier to overcome, since the incidence rates of dry mouth, blurred vision and dizziness were almost twice that seen in the placebo group. It is well-known that compliance to antidepressant therapy is significantly reduced by AE, especially, at an early treatment stage.

Scopolamine has a high affinity for muscarinic (M)3 receptors, which have been proposed to be minimally associated with cognitive impairment in an animal model. However, such evidence is still scarce in human studies, and the relationship between M receptors and cognition is also inconsistent and affected by other complicated factors (e.g., functional activity, selectivity and aging) [11–13]; hence, more confirmative clinical data on this issue are needed. In fact, subtypes of M receptors important for cognitive functions are M1 and M4 in the CNS, while M2 and M3 receptors are associated with AE [11]. In addition, formal assessment tools for cognitive function are also mandatory for evaluation of scopolamine augmentation for treating MDD in subsequent trials, in order to have more direct and informative data about the additional effect of scopolamine augmentation on cognitive functions. A more naturalistic and practical design of switch strategy representing clinical practice should be mandatory for clinician routine practice. A different class of antidepressants other than citalopram should also be tested as standard antidepressants, as there are more than 24 antidepressants on the market today. Finally, other augmentation agents and other treatment strategies such as combination and switching are also effective options for managing initial antidepressant failures. Hence, direct comparison of scopolamine augmentation with different treatment options may also yield intriguing and beneficial findings for clinicians in the management of MDD.

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Key issues

- The efficacy of oral scopolamine augmentation with citalopram was robust in difficult-to-treat major depressive disorder.
- Despite a profound efficacy, small sample size, no use of structured interview and a formal cognitive assessment battery, a higher incidence of adverse events and short-term duration of treatment may limit the results.
- Adequately powered and well-controlled studies are definitely needed to better understand the exact role of scopolamine augmentation for major depressive disorder patients.

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