The muscarinic-cholinergic system as a target in the treatment of depressive episodes in bipolar disorder: a systematic review and meta-analysis

McCaffrey U,[1] Cannon DM,[2] Hallahan B[1,2]

[1]Department of Psychiatry, Galway University Hospital, Galway, Ireland [2] Centre for Neuroimaging & Cognitive Genomics (NICOG), Clinical Neuroimaging Laboratory, NCBES Galway Neuroscience Centre, College of Medicine Nursing and Health Sciences, National University of Ireland Galway

Abstract

Background: Increasing evidence has implicated the cholinergic system as a modulator of mood episodes, including a number of randomised controlled trials (RCTs) demonstrating a putative rapid antidepressant effect of the muscarinic antagonist scopolamine. Here, we review the clinical evidence regarding the three principal cholinergic-modulating agents, scopolamine, biperiden and physostigmine, to establish their effect on mood episodes and better inform potential exploitation of the cholinergic system for mood regulation in major depressive and bipolar disorder. **Methods:** A systematic bibliographic search of double-blind RCTs was conducted between January 1970 and December 2020. A meta-analysis was subsequently performed on 7 studies including 216 participants which satisfied inclusion criteria. **Results:** Administration of scopolamine significantly reduced depressive symptoms as measured by objective mood rating scales with an effect size of -1.095 (95% CI -1.4095, -0.781). Biperiden displayed no significant antidepressant effect. Heterogeneity in study design examining physostigmine prevented meta-analyses for this agent. A systematic review of conducted studies noted anergia and an exacerbation of depressive symptomatology following physostigmine administration, but no obvious anti-manic effect. **Conclusions:** This study suggests that scopolamine may be a potential rapid-acting and efficacious antidepressant agent. Further adequately statistically powered RCTs should be conducted in participants experiencing depressive episodes in the context of major depressive and bipolar disorder to further elucidate any potential treatment and side effects with appropriate follow-up periods to additionally examine durations of treatment response

Introduction

- Current pharmacological treatments used in Bipolar Disorder (BD), particularly for individuals experiencing depressive episodes remain sub-optimal. Consequently, it is critical to develop alternate pharmacotherapeutic strategies to alleviate depressive symptomatology in this patient cohort. Pharmacotherapeutic interventions targeting the cholinergic system represent one potential such strategy, with this system first proposed as having a modulating effect on mood in the 1970s (1).

- The M_2 autoreceptor to date has been the most implicated muscarinic-cholinergic receptor in the aetiology of mood disorders. In individuals with BD, reduced M_2-receptor availability has been suggested from positron emission tomography (PET) studies (2) along with genetic data on polymorphisms in the CHRM2 gene (3). Two M_2-receptor antagonists, biperiden and scopolamine have been studied in a number of small randomised controlled trials in relation to their putative antidepressant effect (4-15). Physostigmine, a cholinesterase inhibitor, has been demonstrated to exacerbate depressive symptomatology in individuals with bipolar disorder in a number of RCTs to date (16-19). Other potential mechanisms have been considered to account in particular for scopolamine's putative antidepressant effect, these include modulation of N-methyl-D-aspartate (NMDA) receptor activity and activation of synaptic plasticity, with scopolamine demonstrated to rapidly increase mammalian target of rapamycin (mTOR) signalling and synaptogenesis (20).

- In a systematic review and meta-analysis, we examined relevant RCTs of two cholinergic antagonists, biperiden and scopolamine and the acetylcholinesterase inhibitor physostigmine, to examine if these agents are associated with improving or exacerbating depressive symptoms in individuals with either BD or Major Depressive Disorder (MDD).

Methods

A systematic bibliographical search of relevant databases (Medline, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL)) was conducted between January 1970 and December 2020 to identify suitable double-blind, placebo controlled RCTs. Criteria for inclusion in the review were studies utilising scopolamine, biperiden or physostigmine as the active agent compared to placebo in human patients with BD or MDD, with objective change in mood being an outcome measure. Studies were excluded if they only used subjective measures of mood or a proxy in place of objective mood measurement instruments. For the meta-analysis, the primary analysis selected an objectively measured reliable psychometric instrument to assess depressive symptomatology, namely the Montgomery-Asberg Depression Rating Scale (MADRS) or the Hamilton Depression Rating Scale (HDRS), (no study included in the meta-analysis utilised both of these psychometric instruments). The mean endpoint measurement during the agent administration phase was compared with the last mean measurement prior to the agent being administered. In studies that utilised swap-over trials, the difference between the beginning and end of only the first phase was compared to eliminate any potential bias due to a lack of washout of the active agent.

For meta-analytic data, effect size for continuous data was calculated by attaining the means, standard deviations and sample sizes for the active and placebo groups for each study. 'Comprehensive Meta-Analysis' Version 3, (Biostat, Englewood, NJ, USA) was used to evaluate any treatment effect between the treatment groups to ascertain the random-model treatment effect (g), with 95% confidence intervals and standard errors for each study undertaken.

Funding and Disclosures: Nil. The authors report no financial or other potential conflicts of interest. As this study utilised existing data, no patient consent/clinical audit consent or ethical approval was required.

Results

Literature Search: A copy of the PRISMA diagram, outlining the search strategy of the literature is presented in Figure 1. Scopolamine was the active agent in nine RCTs (total of ten strata) (7-15), biperiden was the active agent in three RCTs (total of four strata) (4-6) and physostigmine was the active agent in four articles (total of five RCTs) (16-19). **Meta-analysis:** Five scopolamine studies (six strata) and two biperiden studies (three strata) were deemed suitable for meta-analysis. This was conducted on scopolamine and biperiden both together and separately. All studies included in meta-analysis utilised either the HDRS or MADRS to evaluate depressive symptomatology. The results of the meta-analysis are detailed in Figure 2. A statistically significant reduction in depressive symptoms was noted for studies of either scopolamine or biperiden compared to placebo with an effect size (Hedge's g) of -0.802 (95% CI -1.095, -0.509). Scopolamine studies alone (Figure 3) compared to placebo demonstrated an effect size of -1.095 (95% CI -1.4095, -0.781), favouring scopolamine. In contrast, studies of biperiden alone (Figure 4) demonstrated an effect size of 1.159 (95% CI 0.346, 1.972), favouring placebo. When sub-analysed by group, patients with MDD (Figure 5) had an effect of -0.525 (95% CI -1.099, +0.049) while those studies that used a mixed cohort of MDD and BD (Figure 6) had an effect of -0.900 (95% CI -1.241, -0.559). From the data available, it was not possible to examine effects on BD patients as a separate group. Sensitivity analyses based on alternate psychometric instruments (CGI-I, POMS-Depression subscale and HAM-A) demonstrated an overall effect of -0.846 (95% CI -1.166, -0.525) for scopolamine or biperiden studies combined, with scopolamine studies alone demonstrating an effect of -1.074 (95% CI -1.418, -0.73). No physostigmine studies were suitable for meta-analysis or sensitivity analysis due to heterogeneity of study design and measurement of outcomes. **Systematic Review:** Overall, scopolamine produced a rapid antidepressant effect when administered intravenously and was well tolerated with no evidence of mood switching to elation. In one study it was administered orally in combination with citalopram and significantly improved response and remission rates (12). The three studies examining biperiden included a relatively low number of participants. One (IV) biperiden study did note a subjective antidepressant effect but this study was not suitable for meta-analysis (4). Physostigmine did not show an antimanic effect, but did exacerbate depressed mood in patients with MDD in one study (16), along with subjective exacerbation of depressive symptoms in patients with unspecified affective disorder in another (18).

Figures

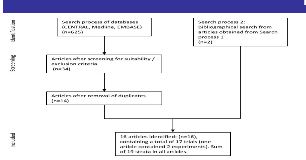

Figure 1. Flow tree for study identification, screening and selection

Figure 2. Meta-analysis of all suitable scopolamine and biperiden strata. Overall effect: Hedge's g -0.802 (-1.095 to -0.509).

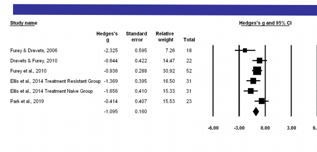

Figure 3. Meta-analysis of all suitable scopolamine strata. Overall effect: Hedge's g -1.095 (-1.409 to -0.780)

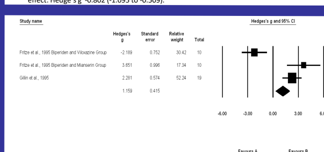

Figure 4. Meta-analysis of all suitable biperiden strata. Overall effect: Hedge's g +1.159 (+0.346 to +1.972).

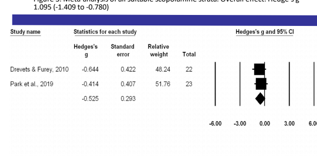

Figure 5. Meta-analysis of suitable strata containing MDD patients only. Overall effect: Hedge's g -0.525 (-1.098 to +0.048)

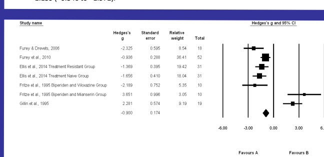

Figure 6. Meta-analysis of suitable strata with mix of MDD+BD patients only. Overall effect: Hedge's g -0.900 (-1.241 to -0.559)

*KEY FOR FIGURES 2-6: 'Favours A' indicates data supports efficacy of active agent.

Discussion and Conclusions

This meta-analysis and systematic review provides preliminary evidence for an antidepressant effect for the M_2-receptor antagonist scopolamine when administered intravenously, with this effect noted within 3-5 days of administration. No such effect was noted for biperiden, with potentially a depressogenic effect evident for physostigmine. Possible reasons for the different findings with scopolamine and biperiden include differential receptor specificity and route of agent administration. Further RCTs utilising a variety of different routes of administration examining specific disorders including depressive episodes in the context of BD or MDD with larger number of study participants, are required to further elucidate if the cholinergic system and in particular scopolamine may provide an additional therapeutic option for individuals experiencing depressive episodes, particularly given scopolamine's potential rapid onset of therapeutic action and good tolerability indices.

REFERENCES: 1. Janowsky DS *et al.* (1972): A Cholinergic-Adrenergic hypothesis of mania and depression. *Lancet* 2:632-635. **2.** Zavitsanou K *et al.* (2005): M_2/M_4 muscarinic receptor binding in the anterior cingulate cortex in schizophrenia and mood disorders. *Brain Res Bull* 65:397-403. **3.** Cannon DM *et al.* (2011): Genetic Variation in cholinergic muscarinic-2 receptor gene modulates M_2 receptor binding in vivo and accounts for reduced binding in bipolar disorder. *Mol Psychiatry* 16:407-418. **4.** Beckmann H, Moises HW (1982): The Cholinolytic Biperiden in Depression: An Acute Placebo Controlled Study. *Arch Psych Neuro Sci* 231:213-220. **5.** Fritze J *et al.* (1995): Cholinergic neurotransmission seems not to be involved in depression but possibly in personality. *J Psychiatry Neurosci* 20:39-48. **6.** Gillin JC *et al.* (1995): No antidepressant effect of biperiden compared with placebo in depression: A double-blind 6-week clinical trial. *Psychiatry Res* 58:99-105. **7.** Newhouse PA *et al.* (1988): The effects of acute scopolamine in geriatric depression. *Arch Gen Psychiatry* 45:906-912. **8.** Gillin JC *et al.* (1991): The effects of scopolamine in sleep and mood in depressed patients with a history of alcoholism and a normal control group. *Biol Psychiatry* 30:157-169. **9.** Furey ML, Drevets WC (2006): Antidepressant efficacy of the antimuscarinic drug scopolamine. *Arch Gen Psychiatry* 63:1121-1129. **10.** Drevets WC, Furey ML (2010): Replication of scopolamine's antidepressant efficacy in major depressive disorder: a randomized, placebo-controlled clinical trial. *Biol Psychiatry* 67:432-438. **11.** Furey ML *et al.* (2010): Scopolamine produces larger antidepressant and antianxiety effects in women than in men. *Neuropsychopharmacology* 35:2479-2488. **12.** Khajavi D *et al.* (2012): Oral scopolamine augmentation in moderate to severe major depressive disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 73:1428-1433. **13.** Ellis JS *et al.* (2014): Antidepressant Treatment History as a Predictor of Response to Scopolamine: Clinical Implications. *J Affect Disord* 162:39-42. **14.** Park L *et al.* (2019): Neurophysiological changes associated with antidepressant response to ketamine not observed in a negative trial of scopolamine in major depressive disorder. *Int J Neuropsychopharmacol* 22(1):10-18. **15.** Zhou J *et al.* (2020): The effects of intramuscular administration of scopolamine augmentation in moderate to severe major depressive disorder: a randomized, double-blind, placebo-controlled trial. *Therap Adv Psychopharmacology* 10:1-11. **16.** Modestin J *et al.* (1973): Uber die depressogene wirkung von physostigmin. *Arch Psych Neuro Sci* 218:67-77. **17.** Shopsin B *et al.* (1975): Rebound phenomena in manic patients following physostigmine. *Neuropsychobiology* 1:180-187. **18.** Janowsky DS *et al.* (1980): Increased vulnerability to cholinergic stimulation in affective-disorder patients. *Psychopharmacol Bull* 16:29-31. **19.** Janowsky DS *et al.* (1986): Central muscarinic effects of physostigmine on mood, cardiovascular function, pituitary and adrenal neuroendocrine release. *Psychopharmacology* 89:150-154. **20.** Voleti B *et al.* (2013): Scopolamine rapidly increases mammalian target of rapamycin complex 1 signaling, synaptogenesis, and antidepressant behavioral responses. *Biol Psychiatry* 74:742-749.