

Results: We managed to group interventions with common ingredients (i.e. common methods, assumptions or structure). In order not to be biased by the retrieved evidence, the interventions were merged “a priori” through a consensus process within the review group, before carrying out the statistical analyses. Results from network meta-analysis were presented as summary relative effect sizes for each possible pair of treatments and ranking probabilities were estimated for all interventions, using the surface under the cumulative ranking curve and mean ranks.

Conclusion: We found that the various psychological interventions in bipolar disorder had common elements that could differentiate these approaches from treatment as usual but also specific elements that could distinguish them from one another.

Galantamine-ER for cognitive deficits in bipolar disorder

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Aims: Subjects with bipolar disorder experience significant cognitive dysfunction, even when euthymic, but few studies have evaluated potential treatments for such deficits. We completed a two-site, 16-week, randomized, placebo-controlled study to evaluate the efficacy of galantamine ER, an acetylcholinesterase inhibitor, for the treatment of cognitive deficits in euthymic subjects with bipolar disorder.

Methods: N = 73 euthymic subjects with bipolar disorder (52% female, age 46.5 years, SD=12.6), who reported subjective cognitive deficits, provided IRB-approved informed consent. 80% of subjects were BPI and 20% BPII. Subjects were randomized 1:1 to adjuvant galantamine ER or placebo (in addition to their existing mood stabilizing treatment) for a 16-week treatment study with flexible doses (8–24 mg/day). At every monthly visit subjects were administered neuropsychological tests of attention (Conners CPT) and self report scales for functional impairment (The Range of Impaired Functioning Tool, LIFE-RIFT). Tests for episodic memory (CVLT) were administered only at baseline and endpoint to reduce learning effects. We used mixed-effects linear regression to compare treatment groups on the repeated assessments of CPT and LIFE-RIFT; changes in CVLT were assessed with ANOVA.

Results: Bipolar subjects treated with galantamine experienced significant improvement in attention (CPT omission and commission errors) compared to placebo over the 16 week treatment, after adjusting for confounders ($p = 0.035$). Galantamine treated patients showed no significant improvement on CVLT or in self-reported functional impairment (LIFE-RIFT) compared to placebo. Galantamine was well tolerated, with rates of adverse effects or new onset mood episodes not significantly different from placebo.

Conclusion: Sixteen weeks of treatment with galantamine ER was associated with significant improvements in measures of attention but not in episodic memory or subjective functional impairment.

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Mood regulatory actions of nucleus accumbens deep brain stimulation

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The mood regulatory mechanisms of deep brain stimulation (DBS) therapy are yet to be fully understood. DBS is shown to have antidepressant actions in severe, treatment-resistant depression (TRD). Interestingly, DBS of mesoaccumbens neurologic targets, including the nucleus accumbens (NAc), have also been shown to induce mania in vulnerable individuals. The nucleus accumbens (NAc) is a critical node in the mesocorticolimbic system and plays a major role in mediating antidepressant behavioral responses in the forced swim test (FST), a preclinical screen for antidepressant efficacy. This study investigates the antidepressant effects of NAc DBS in an established animal model of TRD. Wistar rats were divided into 4 groups: TRD-DBS ($n = 9$), TRD-Sham ($n = 8$), TRD ($n = 10$), and Control ($n = 10$). Bilateral stimulating electrodes were implanted into the NAc of TRD-Sham and TRD-DBS animals. Antidepressant-resistance and depression behaviors were induced through adrenocorticotrophic-hormone (ACTH-(1–24); 100 µg/day; 2nd and 3rd weeks) administration and concurrent social isolation (all 3 weeks) respectively. DBS was administered throughout the 2nd week of ACTH treatment via a back mounted rodent DBS system. 24-hour locomotor activity counts were obtained using infra-red detectors and weekly sucrose preference tests were performed throughout the 3 week protocol. Open field and FST were completed at the end of the 3 weeks. Brains were then removed and stored at -80°C . NAc tissue levels of brain-derived and glial-derived neurotrophic factors (BDNF and GDNF, respectively) were quantified using western blot. Results demonstrate significant increases in locomotor activity for TRD-DBS animals (DBS-Vs-Sham: $p = 0.0248$). Lowered immobility was observed during FST for TRD-DBS animals (DBS-Vs-Sham: $p = 0.0188$). ACTH-induced BDNF expression increased in the outer region substructure NAc-shell ($p = 0.0487$) and decreased in the inner region substructure NAc-core ($p = 0.0275$) compared to controls. These data support antidepressant actions of NAc DBS in TRD. Local changes in neurotrophic factors may contribute to these mechanisms. Importantly, observed increases in locomotor activity over the 3 weeks highlight the potential for mesoaccumbens DBS to impact behaviors such as locomotor activity which may contribute to risk for induction of mania. Preliminary analysis of concurrent effects of daily dopamine reuptake inhibitor GBR12909 (16 mg/kg) administration coupled with NAc DBS demonstrates dopamine-mediated augmentation of these mania-like behaviors.