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Review article

Acetylcholinesterase inhibitors and memantine in bipolar disorder: A systematic review and best evidence synthesis of the efficacy and safety for multiple disease dimensions

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ABSTRACT

Background: Acetylcholinesterase inhibitors (AceI) and memantine might prove useful in bipolar disorder (BD) given their neuroprotective and pro-cognitive effects, as highlighted by several case reports. We aimed to systematically review the efficacy and safety of AceI and memantine across multiple outcome dimensions in BD.

Methods: Systematic PubMed and SCOPUS search until 04/17/2015 without language restrictions. Included were randomized controlled trials (RCTs), open label studies and case series of AceI or memantine in BD patients reporting quantitative data on depression, mania, psychotic symptoms, global functioning, or cognitive performance. We summarized results using a best-evidence based synthesis.

Results: Out of 214 hits, 12 studies (RCTs=5, other designs=7, total n=422) were included. Donepezil (studies=5; treated=102 vs. placebo=21): there was strong evidence for no effect on mania and psychotic symptoms; low evidence indicating no effect on depression. Galantamine (studies=3; treated=21 vs. controls=20) (placebo=10, healthy subjects=10): there was strong evidence for no effect on mania; moderate evidence for no effect on depression; low evidence for no effect on global functioning. Memantine (studies=4; treated=152 vs. placebo=88): there was conflicting evidence regarding efficacy for mania, depression and global functioning.

Limitations: Paucity of RCTs; small sample size studies; heterogeneous design, outcome and patient characteristics.

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Conclusion: There is limited but converging evidence of no effect of AceI in BD, and conflicting evidence about memantine in BD. Too few studies of mostly medium/low quality and lacking sufficient numbers of patients in specific mood states, especially mania, contributed data, focusing solely on short-term/medium-term treatment, necessitating additional high-quality research to yield more definite results.

Contents

1. Introduction

Bipolar disorder (BD) is a chronic mental illness affecting 1–2% of adult population (Weissman et al., 1988), with estimates of up to 4.5% for the spectrum of bipolar disorders (Merikangas et al., 2007). BD seems to be associated with impairments in neurotrophic, cellular plasticity and resilience pathways as well as in neuroprotective processes (Soeiro-de-Souza et al., 2012), supporting the concept that BD is a neurodegenerative disease. However, a precise and specific pathophysiological mechanism underlying BD has not been clarified yet.

Traditional mood stabilizers, namely lithium, carbamazepine and valproate, and antipsychotics are effective for the treatment of acute manic episodes (Cipriani et al., 2013) and for relapse prevention (Miura et al., 2014), while options for bipolar depression are more limited (Thase, 2006). Nevertheless, despite approval of these effective medication treatments, unfortunately up to half of patients have an insufficient response to pharmacotherapy (Calabrese and Delucchi, 1990; Freeman et al., 1992; Pope et al., 1991; Small et al., 1991; Swann et al., 1997). Moreover, naturalistic data suggest that patients spend about half of the time ill during the 2 years following a manic index episode (Jann, 2014). These data stress the need to evaluate other pharmacologic agents for the treatment of BD, which may intersect with specific etiologic pathways that are not targetable with available drugs.

Recently, a catecholaminergic-cholinergic hypothesis has been suggested based on neuroimaging, genetic, and psychopharmacological data, indicating increased cholinergic functioning during depressive phases and increased catecholaminergic (particularly, dopaminergic and norepinephrinergic) functioning during manic phases of BD (van Enkhuizen et al., 2015). Acetylcholinesterase inhibitors (AceI) (donepezil; galantamine; rivastigmine) and memantine, which affect cholinergic transmission among other mechanisms (Drever et al., 2007), are currently used for the treatment of cognitive impairment in Alzheimer's disease (Birks, 2006). Approximately 30–60% of individuals with BD experience a worsening in occupational and social domains after an initial remission of their mood disorder (Kam et al., 2011). Furthermore, BD has been associated with cognitive dysfunction (Torres et al., 2007). Data in older people with BD showing worse information processing speed and executive functioning than age-matched controls (Gildengers et al., 2007) could suggest that these individuals are at higher risk of cognitive problems particularly during late-life. In this context, the use of memantine might be appropriate since this drug is commonly used in moderate-severe forms of Alzheimer's disease and seems to have neuroprotective effects (Lopes et al., 2013). Moreover, based on uncontrolled observations and case reports, memantine seems to also have potential anti-manic and mood stabilizing effects (Serra et al., 2014c) making it an interesting intervention for BD.

Until now, evidence suggests that the use of donepezil in schizophrenia yields no effect (Keefe et al., 2008), while galantamine seems to improve some cognitive domains (Buchanan et al., 2008; Lee et al., 2007; Schubert et al., 2006), particularly in combination with antipsychotics; however evidence is still weak due to the limitations of included studies (Singh et al., 2012). Similarly, a systematic review (Zdanys and Tampi, 2008) did not find conclusive results for the use of memantine in several psychiatric disorders, including depression, schizophrenia, obsessive–compulsive disorder, substance abuse, pervasive developmental disorders, and binge eating disorder. The same authors found limited evidence for memantine in BD although this conclusion was limited to findings from case-reports (Zdanys and Tampi, 2008).