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Short communication

Differential response to lithium between melancholic and non-melancholic unipolar depression

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ABSTRACT

The purpose of this report was to review the evidence regarding the differential response to lithium treatment between patients with unipolar melancholic and non-melancholic depression. Three studies suggest that the prophylactic effect of lithium in maintenance treatment may be greater in melancholic depression. Another study reported that melancholic symptoms, such as weight loss and psychomotor disturbances, predict a better response to lithium augmentation. These preliminary data suggest that the response to lithium may be greater in melancholic than in non-melancholic depression, which could be the focus of further research.

1. Introduction

Melancholia (also named primary, endogenous, vital, or endogenomorphic depression) was traditionally described as a subtype of a depressive episode characterized by pervasive anhedonia with lack of mood reactivity, psychomotor disturbances, and typical vegetative symptoms (including early morning waking, diurnal variation with worse mood in the morning and weight loss). We have recently published in this journal a quantitative review on outcome-to antidepressants in major depressive disorder (MDD) with melancholic features (Valerio et al., 2018). One of the main findings of this meta-analysis was that although there was no difference in the odds of responding to antidepressants between melancholic and non-melancholic MDD (OR 0.95, 95% CI 0.77 to 1.18), response to placebo was lower in the former (OR 0.17, 95% CI 0.04 to 0.68). Although we recognize the preliminary nature of these results as a consequence of the scarcity of studies on this topic, a possible interpretation is that the "true" antidepressant effect (the extent to which active-drug outperform placebo) could be greater in melancholia.

The differential profile of outcome-to-treatment in unipolar depression might not be limited to antidepressants but might instead be extended to other drugs commonly used in the management of MDD such as lithium. In fact, while the role of monotherapy with lithium for acute unipolar depression is controversial, its usefulness as augmentation strategy to antidepressant treatment and in the prophylaxis of MDD has been well documented (for review see Bschor, 2014 and Abou-Saleh et al., 2017). Therefore, the aim of this report was to summarize the evidence assessing the influence of melancholic features on the response to lithium in MDD.

2. Methods

Articles published in peer-reviewed English language journals were retrieved from the online databases Pubmed/PsychInfo using combinations of the following keywords: lithium AND depressi* OR melanchol* OR endogeno*. The reference lists of the studies identified for inclusion were also reviewed for additional relevant reports. If there were studies with overlapping content based on the same patient sample, only the data from the study with the largest sample were considered.

3. Results

To the best of our knowledge, no clinical trial evaluating the efficacy of lithium for the acute treatment of MDD considered melancholic features as potential moderators of outcomes.

Regarding the maintenance treatment, in a sample of patients attending to a lithium clinic, Abou-Saleh and Coppen (1986) explored endogenous subtype of unipolar depression as a predictor of response to prophylactic lithium. Outcome was assessed using the Affective Morbidity Index (AMI), a measure of both the time spent with and the severity of an episode, and depression subtype was assessed through the

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Newcastle Scale, on which higher scores indicate endogenous depression. During the first year and the additional 2-year follow-up patients with higher scores on the Newcastle Scale had significantly lower AMI. Furthermore, unipolar patients with the highest scores on the Newcastle Scale showed better outcomes with prophylactic lithium than bipolar patients. In another study, Maj et al. (1985) found that psychomotor retardation and the melancholic subtype of MDD (defined by DSM-III criteria) were predictors of good response to maintenance treatment with lithium during a 2-year follow-up period. In their study, good response was defined by the absence of relapses requiring hospitalization and/or treatment with additional specific drugs. Finally, in a more recent study Serretti et al. (2000) reported a significant correlation between the number of those considered as melancholic symptoms (slowed activity, diurnal variation, excessive self-reproach, and early morning waking) and the reduction of episode frequency after the initiation of prophylactic lithium. Nevertheless, the latter was performed on a mixed sample of unipolar and bipolar patients, and specific conclusion about unipolar depression cannot be extracted.

Finally, another study showed a relationship between response to lithium augmentation and melancholic features. In a sample of 105 patients with unipolar depressive episode resistant to tricyclic antidepressants, baseline weight loss and psychomotor disturbances in the Newcastle Scale were predictors of clinical remission to lithium augmentation (Alvarez et al., 1997).

4. Discussion

Although the initial reports of Baastrup and Schou (1967) demonstrating the prophylactic efficacy of lithium for mood disorders included patients with endogenous (or equivalently melancholic) unipolar depression, since the inclusion of the MDD category in the DSM-III in 1980 very few studies evaluated melancholic features as moderators of response. Consistent with the results of our meta-analysis on antidepressants, the studies reviewed in this report seem to show that the response to lithium could also be greater in patients with melancholic unipolar depression.

Of course, the scarcity of studies on this topic is a main limitation to draw more firm conclusions. The results on the response to lithium prophylaxis should also be interpreted in the context of studies showing that some patients with recurrent depression have some episodes that are melancholic and some others that are not (Angst et al., 2007; Merlatin et al., 2004). The lack of longitudinal stability across illness episodes does not escape the controversy over whether the melancholic and non-melancholic depressions represent two etiologically distinct subtypes of MDD or one subtype differing in severity (with melancholia being only a more severe form of depressive episode). Some authors suggest that the criteria of the melancholic specifier of the DSM-IV could lead to an overdiagnosis of melancholia, with the consequent failure to differentiate it from other subtypes of major depressions (Fink et al., 2007; Parker, 2011). Therefore, either the severity hypothesis or the questionable value of the DSM-IV melancholic specifier could contribute to explain the lack of longitudinal stability across illness episodes (Angst et al., 2007; Merlatin et al., 2004). The nosological positioning of melancholia or which are the best criteria to identify it exceeds the scope of this report. However, it should be noted that a better response to lithium would be plausible whether melancholia was a more severe form of depression or if it was a discrete clinical entity.

All things considered, it worth noting the shortcomings that the concept of MDD could imply for clinical trials: 1) it would not allow to identify differences in response to a given therapeutic intervention between episodes with and without melancholic features, and 2) it could contribute to heterogeneity of results between studies depending on the proportion of included patients with and without melancholic features. Therefore, it would be desirable to conduct future studies specifically designed to test the differences in therapeutic responses (both to pharmacological and psychosocial interventions) between patients with melancholic and non-melancholic MDD. In the meantime, it would be valuable if trials including patients with MDD would at least perform a sub-analysis of response to the active-intervention and placebo between these subtypes of the disorder. Melancholia appears as an interesting target to improve our knowledge about personalized medicine of MDD.

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Conflict of interest

None.

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