Limitations of evidence base for prescribing aripiprazole in maintenance therapy of bipolar disorder

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The evidence base for the prescribing of aripiprazole in maintenance treatment of bipolar disorder is limited to a single trial, sponsored by the manufacturer of aripiprazole, according to a rigorous appraisal of the evidence for its use led jointly by Alexander Tsai of Harvard University, Boston USA, and Nicholas Rosenlicht of the University of California San Francisco, USA. In the paper, published in this week's *PLoS Medicine*, the authors describe key limitations of the trial, which were not identified in most subsequent review articles and guidelines for the treatment of bipolar disorder in which the trial was cited.

Bipolar disorder (also known as manic depression) is a common and serious psychiatric illness. Individuals with bipolar disorder experience mood swings with manic episodes (where they may feel euphoric, restless, and behave impulsively), along with depressive episodes where they may feel low, worthless, and suicidal. Aripiprazole is a second-generation antipsychotic medication and the newest of such drugs to have received approval by the US Food and Drug Administration (FDA) for use both in treatment of acute episodes and, more recently, for maintenance therapy.

Drs. Tsai and Rosenlicht and their colleagues conducted a systematic search to find all published and unpublished studies relating to use of aripiprazole for maintenance therapy of bipolar disorder, including a request to the FDA under Freedom of Information Act legislation. They

critically appraised this evidence and then used citation searches to examine how the primary evidence was subsequently referenced in the medical literature. The authors found only a single trial describing the use of aripiprazole during the maintenance phase of bipolar disorder. Further, they found significant limitations of this trial that constrain its interpretation as supporting the use of aripiprazole for this indication. First, the trial duration was too short to show that the drug was truly helpful in maintaining initial benefit or preventing mood swings over the long term. Second, very few participants in the trial completed the entire study. Third, the trial was based on a select minority of subjects who had shown an initial response to the drug, making it difficult to extrapolate these findings to patients with bipolar disorder more widely. Fourth, the trial had a design whereby patients assigned to placebo were abruptly taken off aripiprazole treatment given to them during a previous "run-in" phase and reassigned to placebo; differences in risk of relapse seen between trial arms may thus also reflect the potentially harmful effects of rapid drug withdrawal in patients given placebo.

Despite these shortcomings, the authors found that this single trial was subsequently cited by 104 review articles and treatment guidelines, with very few mentioning the study's limitations.

The authors comment that "…alternative modifications or study designs may improve the probability of generating more useful data from studies in this vulnerable patient population to inform the treatment of similar patients in the future."

Patients (or their family members) who may learn of this study's findings are urged to contact their physician if concerned about what these findings may mean for their treatment. Specifically, the findings do not mean patients should cease their medication; despite the limitations of the evidence described here, this drug may be helpful to them. In addition, the study did not assess the evidence for the use of

aripiprazole in acute treatment of bipolar disorder.

More information: Tsai AC, Rosenlicht NZ, Jureidini JN, Parry PI, Spielmans GI, et al. (2011) Aripiprazole in the Maintenance Treatment of Bipolar Disorder: A Critical Review of the Evidence and Its Dissemination into the Scientific Literature. PLoS Med 8(5): e1000434. doi:10.1371/journal.pmed.1000434

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