Journal of Affective Disorders 191 (2016) 187–208

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

A meta-analysis of efficacy and safety of aripiprazole in adult and pediatric bipolar disorder in randomized controlled trials and observational studies

Martina Meduri [a,1], Giorgia Gregoraci [b,1], Valentina Baglivo [a], Matteo Balestrieri [a], Miriam Isola [b], Paolo Brambilla [c,d,*]

[a] Department of Experimental and Clinical Medical Sciences, ICBN, University of Udine, Udine, Italy
[b] Department of Biological and Medical Sciences, University of Udine, Udine, Italy
[c] Department of Neurosciences and Mental Health, Psychiatric Clinic, Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy
[d] Department of Psychiatry and Behavioural Sciences, University of Texas Health Science Center at Houston, TX, USA

ARTICLE INFO

Article history:
Received 14 August 2015
Received in revised form
27 October 2015
Accepted 17 November 2015
Available online 1 December 2015

Keywords:
Safety
Sedation
Akathisia
Weight gain
Extrapyramidal symptoms
Gastroenteric symptoms
Hyperprolactinemia
Lithium
Haloperidol

ABSTRACT

Background: Aripiprazole (ARP) has been shown to be effective in the treatment of bipolar disorder (BD). However, no prior investigation considered both randomized clinical trials (RCTs) and non-RCTs. We here evaluated the efficacy and safety of ARP compared with placebo (PCB) and other drugs at 3- and 12-weeks in adult and pediatric population including, for the first time, both observational and controlled studies.

Methods: All studies were systematically located by searching electronic sources (EMBASE, MEDLINE, CINHAIL, PsychINFO, Cochrane Central Register of Controlled Trials, Scopus and ClinicalTrials.gov) till June 30th, 2015. The primary outcome was ARP efficacy (mean change from baseline in Young Mania Rating Scale); secondary outcomes regarded acceptability and safety. Results Sixteen RCTs and 6 non-RCTs met our inclusion criteria; 2505 and 2932 patients were included in the analyses of acute and stabilization phase, respectively. In both the acute and stabilization phases ARP efficacy was superior to PCB and comparable to other drugs. The safety profile was similar to other drugs considering in particular sedation, akathisia, weight gain, extrapyramidal and gastroenteric symptoms, with a significant lower risk of hyperprolactinemia particularly at 12-weeks.

Limitations: Data on failed trials are generally limited.

Conclusions: ARP resulted to be an effective treatment in children and adults with BD at 3- and 12-weeks both in a controlled experimental setting or in the real world clinical practice, being poorly associated with hyperprolactinemia. Larger studies are needed to confirm our results related to the maintenance phases and to the pediatric bipolar population.

1. Introduction

Bipolar disorder (BD) refers to a group of affective disorders characterized by marked mood swings between mania and depression, leading to significant personal distress or social dysfunction (Phillips and Kupfer, 2013). It is a chronic and recurrent illness with a lifetime prevalence rates between 0.3–1.5% in the general population (Stern et al., 2015), being amongst the top 30 causes of disability worldwide and associated with significant healthcare costs (Weissman et al., 1996; NICE Clinical Guidelines, 2014). The exact pathogenesis is still unknown and thought to be multifactorial, including genetic basis, biological factors (e.g., neurotransmitters and hormones) and environmental influences (Craddock and Sklar, 2013). The treatment of BD is complex due to the presence of psychiatric comorbidities, heterogeneous configurations of episodes and low patients' compliance. Even though psychological and psychosocial interventions may have an important part to play (Goodwin et al., 2007), the primary treatments are pharmacological (Brambilla et al., 2001,

Abbreviations: FDA, Food and Drug Administration; EMA, European Medicines Agency; 5HT1A-5HT2A, 5- hydroxytryptamine receptors; D2, Dopamine Receptor D2

* Correspondence to: Dipartimento di Neuroscienze e Salute Mentale, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Francesco Sforza 35, 20122 Milano, Italy.
E-mail address: paolo.brambilla1@unimi.it (P. Brambilla).
[1] The two authors contributed equally to this study.

http://dx.doi.org/10.1016/j.jad.2015.11.033
0165-0327/

Yatham et al., 2013). Such treatments have widely broadened in the last few years, partly thanks to the introduction of Second Generation Antipsychotic drugs (SGA) (Brambilla et al., 2003; McIntyre et al., 2011; Vieta and Valentí, 2013; Yatham et al., 2009). These share similar, but faster efficacy than the older antipsychotics in mania, and have been reported to have better adverse event profiles, specifically in relation to extrapyramidal side effects (Yatham et al., 2013). Aripiprazole (ARP) is a recent FDA- and EMA-approved SGA and it is known to have favorable efficacy and tolerability for the treatment of BD (Aitchison et al., 2009; McIntyre et al., 2007), both in adult and pediatric population (NICE, 2014). It is a partial agonist of dopamine D2 and serotonin 5-HT1A receptors and an antagonist of 5-HT2A receptors, with a distinct receptor-binding profile compared to other SGA (Burris et al., 2002). This unique mechanism of action, the lack of significant affinity for muscarinic and histaminergic receptors, and its low affinity for alpha-adrenergic receptors, may account for its low frequency of common antipsychotic adverse events (i.e., extrapyramidal symptoms, tardive dyskinesia, weight gain, sedation, hyperprolactinemia, QTc prolongation, hyperglycemia, and hyperlipidemia) (Goodnick and Jerry, 2002). To the best of our knowledge, meta-analyses on ARP were based only on RCTs (Arbaizar et al., 2009; Brown et al., 2013; Fountoulakis et al., 2009, 2011). Fountoulakis et al. (2009) supported the usefulness of ARP in the treatment of the psychotic symptoms during the acute manic and maintenance phases. Moreover, Fountoulakis et al. (2011) and Arbaizar et al. (2009) evaluated the efficacy of ARP in the treatment of BD, as monotherapy and as monotherapy add-on, respectively. In Fountoulakis et al. (2011) ARP resulted to be useful during all phases of bipolar illness, although its effect against acute bipolar depression was weak and during the maintenance phase was proven only in manic patients who responded to ARP during the acute phase. Finally, Brown et al. (2013) reported that ARP was effective in the treatment of acute manic and mixed episodes in adults, children and adolescents in monotherapy or in combination with other antimanic drugs. Because of the lack of knowledge in the use of ARP in real-world clinical settings, we performed a systematic review and a meta-analysis on ARP efficacy and tolerability in adult and pediatric population in the acute and maintenance phases, including both RCTs and observational (non-RCTs) studies in order to provide a more comprehensive evidence on ARP use in every day clinical psychiatry.

2. Objectives

To assess the efficacy and tolerability of ARP alone or in combination with other antimanic drug treatments, compared with placebo (PCB) and other drug treatments, in alleviating symptoms of manic, mixed or depressive episodes at 3- and 12-weeks. Other objectives included reviewing the tolerability of treatment with ARP and investigating the adverse effects of ARP treatment. Finally, we provided a qualitative systematic review of evidence that cannot be quantitatively summarized.

3. Methods

3.1. Search strategy, inclusion and exclusion criteria

We reviewed available literature on the efficacy, safety and acceptability of ARP alone or in combination in alleviating symptoms of manic, mixed or depressive episodes during the acute and post-acute phases in adults and children with a diagnosis of BP type I or II according to criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV/DSM-IV-TR), of International Classification of Diseases, Tenth Revision (ICD-10), as well as of ICD-9 and of DSMIII/DSM-III-R. We systematically searched electronic sources till June 30th, 2015, using EMBASE, MEDLINE, CINHAIL, PsychINFO, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, ClinicalTrials.gov, then used hand-search through references of other systematic reviews and meta-analyses. Conceptual search framework was as below:

(("bipolar disorder" OR (Manic-depressive AND psychos*) OR Mania) AND (abilify OR "OPC 14597" OR OPC-14597 OR aripiprazole))

We chose not to restrict our search to randomized controlled trials (RCTs) and we planned to include observational and non-randomized studies in the quantitative evaluation, if their design was comparable to that of RCTs in terms of patients' selection and dose regimen, and except for randomization and blinding. This choice was driven by the awareness that RCTs settings are very restrictive and provide an ideal profile of the drug that can result different in the clinical practice.

3.1.1. Types of studies

We included randomized controlled trials (RCTs), retrospective and prospective observational studies that compared ARP with PCB or other active treatments. The choice of including also non-RCT studies was driven by the intention to provide a less ideal profile of the study drug (Borenstein et al., 2009; Brambilla et al., 2002; Zwahlen et al., 2008). For trials with a crossover design only results from the first randomization period were considered. Only English language articles were included.

3.1.2. Types of participants

Patients of both sexes and all ages with a diagnosis of bipolar or schizoaffective disorder (manic or mixed episode, with or without psychotic symptoms) and all subtypes of BD (Type I and II, rapid cycling and other) were included. We planned to separate data into diagnostic groups when trials involved heterogeneous groups of patients, such as schizoaffective disorder and recurrent unipolar depression; however, that was not possible because in most cases insufficient information was provided. Studies of acute treatment with ARP that recruited patients with diagnoses other than bipolar disorder or schizoaffective disorder or that did not stratify according to diagnosis were not included in this review. Only studies reporting the total number of patients experiencing side effects during the study period, or reporting the number of patients experiencing individual side effects, were retained.

3.1.3. Types of interventions

Comparisons included ARP vs. PCB and ARP vs. other drugs. Because of the relatively low number of studies available for each comparison, any ARP treatment was considered as intervention group (either APR alone or ARP in combination with other antimanic drugs, both in adults or in children). However, because the ARP groups were not homogeneous, we also performed subgroup analyses. Comparison groups were on PCB or on other antimanic drugs, and separate analyses were performed for each.

3.2. Data collection, data extraction and management

Two review authors (MM and VB) examined the titles and abstracts of citations obtained from the searches. Any article indicating that a relevant study may be described was retrieved for assessment. The two reviewers independently assessed articles for inclusion according to the previously defined inclusion criteria. In case of disagreement a third author (PB or GG) was contacted after discussion. The same two authors independently performed the quality assessment using the Cochrane Method Guidelines for Systematic Reviews (Higgins and Green, 2011) for evaluating RCTs