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Aripiprazole augmentation, antidepressant combination or switching therapy in patients with major depressive disorder who are partial- or non-responsive to current antidepressants: A multi-center, naturalistic study

Changsu Han [a,1], Sheng-Min Wang [b,1], Ho-Jun Seo [b], Boung Chul Lee [c], Hong Jin Jeon [d], Won Kim [e], Kyung-Phil Kwak [f], Chi-Un Pae [b,g,*]

[a] Department of Psychiatry, College of Medicine, Korea University, Seoul, Republic of Korea
[b] Department of Psychiatry, The Catholic University of Korea College of Medicine, Seoul, Republic of Korea
[c] Department of Neuropsychiatry, College of Medicine, Hallym University, Seoul, Republic of Korea
[d] Department of Psychiatry, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[e] Department of Psychiatry, College of Medicine, Inje University, Seoul, Republic of Korea
[f] Department of Neuropsychiatry, School of Medicine, Dongguk University, Gyeongju, Republic of Korea
[g] Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, 2218 Elder St., Duram, NC, USA

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ABSTRACT

There has been no studies comparing the clinical benefits of aripiprazole augmentation (AT), antidepressant combination (AC), and switching to a different antidepressant (SW) in patients with major depressive disorder (MDD) patients partially or not responding to an initial antidepressant. AT, AC, or SW was chosen by patients. The primary efficacy measure was the proportion of patients showing an improvement in the Clinical Global Impression-Clinical Benefit (CGI-CB) score at week 8. Secondary efficacy measures included changes in CGI-CB, CGI-Severity (S) and subjective satisfaction scores. Remission and responder analysis were also employed. A total of 295 patients were enrolled. The most preferred strategy was AT ($n = 156$, 52.9%), followed by AC ($n = 93$, 31.5%) and SW ($n = 46$, 15.6%). The improver was significantly higher in AT (74.1%) compared with AC (48.1%; $p < 0.001$) and similar to SW (73.5%, $p = 0.948$), whereas no significant difference was found between AC and SW. Similar results were also found in the most secondary endpoint measures proving a superiority of AT over AC without differences between AT and SW. Tolerability profiles were similar across the three groups; however, the mean weight gain for SW (−0.1 kg) was significantly less than that for AC (1.3 kg, $p < 0.05$). Patients preferred AT to AC or SW when an antidepressant was ineffective in treating their depression. Among the three treatment strategies, overall AT yielded greater clinical benefit than did AC and SW. Adequately powered, well-controlled clinical trials are strongly warranted to confirm our findings due to methodological shortcomings.

1. Introduction

Most currently available treatment guidelines suggest that antidepressant non-responders or partial responders should be switched to a different antidepressant or receive a second antidepressant or non-antidepressant agent such as lithium, atypical antipsychotics (AAs), or thyroid hormone in combination with the initial antidepressant (Anderson et al., 2008; Bauer et al., 2013; Kennedy et al., 2001; Patkar and Pae, 2013).

The superiority of one treatment modality over the other has not yet been established in patients with major depressive disorder (MDD) who do not respond to antidepressants (Connolly and Thase, 2011). Additionally, insufficient empirical evidence is available with antidepressant combining or switching strategies (Kohler et al., 2013; Pae et al., 2011b, 2012; Papakostas et al., 2008; Rush et al., 2011; Thase, 2011). Thus, augmenting AAs is becoming common practice in partially or non-responsive patients with MDD

* Corresponding author. Department of Psychiatry, Bucheon St. Mary's Hospital, The Catholic University of Korea College of Medicine, 2 Sosa-Dong, Wonmi-Gu, Bucheon 420717, Kyeonggi-Do, Republic of Korea. Tel.: +82 32 340 7067; fax: +82 32 340 2255.
E-mail address: pae@catholic.ac.kr (C.-U. Pae).
[1] Equally contributed to the paper as the first author.

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based on results from a number of well-designed, placebo-controlled clinical trials (RCTs) (Han et al., 2013a, 2013b; Pae and Patkar, 2013). Among AAs, aripiprazole was the first drug to be approved by the US FDA to treat MDD as an augmentation therapy in 2007 (Pae et al., 2011a). Aripiprazole's augmentation effects in depressed patients were clearly shown in numerous randomized, controlled clinical trials (RCTs) and meta-analyses (Berman et al., 2009, 2007; Marcus et al., 2008; Nelson and Papakostas, 2009). Though aripiprazole augmentation has been shown to be safe and well tolerated (Berman et al., 2009, 2007; Marcus et al., 2008), augmenting AA therapy may increase the risk for various adverse events (AEs); for example, the incidence of akathisia and restlessness in patients whose antidepressant therapy was augmented with aripiprazole was high in such RCTs (Pae et al., 2011a).

The best available treatment should be able to improve residual symptoms and remit depression, whereas imprudent treatment may lead to a more chronic and morbid clinical course (Rush et al., 2006). To enable effective treatment choices for patients with MDD, evidence from both RCTs and naturalistic trials in routine practice settings is useful and necessary. Furthermore, although RCTs are considered to provide the strongest empirical support, their biases in patient selection can limit generalizability, and blinded use of placebos can influence treatment response (Kaptchuk, 2001; Severus et al., 2012).

In this context, a recent naturalistic study showed that AA or lithium augmentation was more effective than combining or switching antidepressants, but the sample size was relatively small (total $n = 98$ in four groups), and the treatment strategy was determined by the treating physician (Kohler et al., 2013). Furthermore, the 28 patients whose antidepressant was augmented with an AA received any of seven AAs, preventing investigation of the clinical utility and tolerability of a particular AA. To the best of our knowledge, the clinical benefit of augmenting with a particular AA has not been compared with that of combining or switching antidepressants, nor has patients' preference among these three strategies been examined.

Therefore, we chose a naturalistic study design for our comparison of aripiprazole augmentation therapy (AT), antidepressant combination (AC), and switching to a different antidepressant (SW) in patients with MDD who were partially or non-responsive to current antidepressants.

2. Methods

2.1. Study design

This was an 8-week, prospective, patient preference-based, multicenter, open-label, flexible-dose study comparing the clinical benefits of AT, AC, and SW in a naturalistic treatment setting.

2.2. Subjects

Diagnoses were made on the basis of clinical assessments by experienced and board-certified psychiatrists. The subjects included were ≥20 years, meeting diagnosis of MDD according to DSM-IV TR criteria, who were partial- or non-responsive to initial antidepressant recruited in all outpatient clinic basis. The partial- or non-responsive to current antidepressants were defined by clinical judgement and Clinical Global Impression-Severity (CGI-S) score of ≥2 (Papakostas et al., 2005) at the enrollment point since the CIS-S score of 2 corresponds to the Montgomery–Åsberg Depression Rating Scale score of 11 (Bandelow et al., 2006) despite an adequate antidepressant dosage for more than 8 weeks.

Patients were excluded if they were pregnant or nursing or if they reported substance abuse or dependence within the past 12 months. Additionally, patients diagnosed with unstable medical or neurological disorders were excluded (participation was allowed if the clinical condition was stable for more than 3 months under routine therapeutic medications, e.g., hypertension). Patients were also excluded if they had psychotic symptoms, met criteria for an Axis I diagnosis of delirium, dementia or other cognitive disorder, bipolar disorder, schizophrenia, or other psychotic disorder. Other reasons for study exclusion included the following: first onset depressive episode, serious suicidal risk, hospitalization because of depression within 2 months of study entry, current treatment with cognitive behavioral therapy, history of electroconvulsive therapy to treat the current episode, and participation in other clinical trials within 1 month.

2.3. Strategy choice procedure

Investigators informed patients of the nature of the present study. Patients meeting inclusion criteria chose either AT, AC or SW after receiving complete information on the risks/benefits of each treatment strategy. Patients were also given guidance on the factors on how clinicians consider when choosing a treatment strategy (e.g., patients' medical and psychiatric needs, cost, history of response and compliance, and risk of suicide or overdose, as well as each drug's regulatory agency approval, tolerability and AEs, and potential interactions with other medications). To minimize the influence of the treating physician, the personal opinion of the investigator was not conveyed to the patient.

2.4. Medication

In both AT and AC groups, the dose of initial antidepressant was maintained on the same dose during the study. In AC and SW groups, the dose of second antidepressants was flexibly titrated at the discretion of the investigator based on clinical response and AEs.

The dose of aripiprazole as an adjunct treatment was 2–15 mg/day according to the product label approved by Korean FDA. Titration by the investigator was fully dependent on clinical response and tolerability during the study. The name and dose range of initial antidepressants were as follows: Bupropion XL 300 mg/day, duloxetine 60 mg/day, escitalopram 10–20 mg/day, fluoxetine 20–40 mg/day, mirtazapine 15–45 mg/day, milnacipran 25–100 mg/day, paroxetine controlled release (CR) 25–62.5 mg/day or paroxetine 20–40 mg/day, sertraline 100–150 mg/day, tianeptine 25–37.5 mg/day, and venlafaxine immediate or extended release (IR or ER) 112.5–225 mg/day.

In all three groups, patients did not receive mood stabilizers, other augmentation agents such as psychostimulants, thyroid hormones, and dopamine agonists, or antipsychotics other than aripiprazole during the study. Benzodiazepines, antiparkinsonian drugs, propranolol (maximum 60 mg/day), and zolpidem were permitted as needed at the discretion of the investigator for control of anxiety, to prevent or reduce extrapyramidal symptoms (EPSs), to control akathisia, or for sleep control, respectively. Other concomitant medical drugs such as digestive aids and analgesics were allowed.

This study was conducted from December 2010 to March 2012 and involved seven university-based teaching hospitals in Korea. The study was approved by the relevant institutional review board at each center and was conducted in compliance with the Declaration of Helsinki (IRB:HC10OIME0079). All patients provided informed consent.

2.5. Effectiveness and tolerability

At baseline and week 8, clinical benefit was evaluated using the CGI-Clinical Benefit (CGI-CB), and severity of patients' clinical