Aripiprazole augmentation for major depressive disorder: dosing patterns in a naturalistic treatment setting

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This study investigated the dosing patterns for aripiprazole augmentation for major depressive disorder (MDD) in a naturalistic treatment setting. Between 1 January 2009 and 31 March 2012, patients with a diagnosis of MDD who were receiving aripiprazole augmentation in conjunction with an ongoing antidepressant were recruited for this study. The electronic medical records and clinical data for a total of 276 patients were reviewed up to a year. The mean duration of aripiprazole augmentation was ~5 months; the mean time to the first increase of aripiprazole was about 3 weeks; and the mean initial, first up-titrated, maximal, and maintenance doses were 3.4, 4.2, 4.7, and 4.4 mg/day, respectively. The most frequent adverse events were insomnia, followed by anxiety and sedation. The current results indicate that the actual doses of aripiprazole augmentation with ongoing antidepressant for MDD should be lower than the doses used in placebo-controlled clinical trials and those recommended by the US Food and Drug Administration. Adequately powered and well-controlled prospective studies are needed to better understand the exact role of low doses of aripiprazole augmentation in the treatment of MDD, particularly in routine practice. *Int Clin Psychopharmacol* **29:116–119 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

An increasing number of small-scale case reports and open-label studies evaluating the effectiveness and tolerability of aripiprazole augmentation for major depressive disorder (MDD) has prompted randomized, placebo-controlled clinical trials (RCTs) (Berman *et al.*, 2007, 2009; Marcus *et al.*, 2008). These controlled trials have consistently reported a significant improvement in depressive symptoms, and their results favor the use of aripiprazole augmentation over placebo. In addition, remission rates were significantly higher with aripiprazole augmentation than with placebo in all three RCTs (ranges: −10.2 to −17.9%), and remission was achieved in significantly more patients taking aripiprazole augmentation versus placebo as early as week 1 (Berman *et al.*, 2007) and week 2 (Marcus *et al.*, 2008) of treatment. On the basis of these clinical trial data, aripiprazole was the first drug approved by the US Food and Drug Administration (FDA) to augment antidepressants in the treatment of patients with MDD.

Although well-designed RCTs may be the gold standard for proving the efficacy of a drug, these trials also have clear limitations when translating the results into routine practice. This is because of inherent shortcomings such as the inclusion of a highly selective patient population, an overexclusion of patients, a forced dose titration of the active drug, and outcome measures that are too oriented toward research goals, which typically do not reflect the situation of busy routine practice (Pae *et al.*, 2012). Furthermore, previous studies investigating the use of atypical antipsychotics in psychiatric practice have clearly indicated that prescribed doses for a particular drug may differ considerably from those recommended on the package insert label (Hartung *et al.*, 2008).

The inclusion of real-world treatment issues in research studies would assist clinicians in addressing how to efficiently utilize certain medications under approved indications, particularly if limited information is available following the market launch of that drug. Hence, the present study is an investigation into dosing trends of aripiprazole augmentation during the treatment of patients with MDD in a routine practice.

Methods

Between 1 January 2009 and 31 March 2012, patients with a diagnosis of MDD who were receiving aripiprazole augmentation in conjunction with an ongoing antidepressant were recruited for this study. Depression was defined according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision using clinical modification codes F32.X (not including F33.X and F31.X).

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Data for all patients were collected from the electronic medical records (EMR) of a specialized depression outpatient clinic at a university-affiliated hospital. A new prescription (index prescription point) of aripiprazole was defined as the first prescription of this drug with the patient having had no previous prescriptions for aripiprazole augmentation. The follow-up visit was verified using the prescription date and actual days of prescription. Following data collection, each patient was tracked for up to 1 year after the index prescription point. Follow-up data collection was discontinued if the patient switched to another augmentation agent, did not receive further aripiprazole augmentation, was observed to have poor compliance (on the basis of EMR description: less than 70% intake of immediate previous prescription pills), or had a gap between outpatient clinic visits of longer than 1 month. All data were collected independently by two investigators and subsequently verified and approved for data mining by the same investigators. EMRs were reviewed for the following clinical and demographic variables: age; sex; duration of aripiprazole augmentation; initial, first up-titrated, maximal and maintenance doses of aripiprazole; presence of previous treatment strategy; type of ongoing antidepressant; prophylactic use of antiparkinsonian drugs (ADs); new use of ADs during follow-up period; adverse events (AEs); continuation or discontinuation of aripiprazole; mean time to augmentation; and mean time to increasing the initial dose of aripiprazole. The average daily dose of aripiprazole was calculated as the sum of the number of pills per day multiplied by dose and then divided by the sum of the number of days of prescription. Duration of aripiprazole augmentation was calculated using the total sum of prescription days.

The Bucheon St Mary's Hospital Institutional Review Board approved the study and all data were collected using data extraction forms with deidentified features of the patients (IRB approval number: HC13RISI0073).

Descriptive statistics are presented as means (SDs) and numbers (percentages) for continuous and categorical variables, respectively. Statistical analysis was carried out using NCSS 2007 Power Analysis and Sample Size Software (NCSS, LLC, Kaysville, Utah, USA).

Results

On the basis of the selection criteria, the EMRs of 276 patients were reviewed, and their clinical and demographic data were collected (Table 1). Briefly, the majority of patients were women (~72%) and their mean age was 39 years. The most frequently used ongoing antidepressant agents were venlafaxine, followed by escitalopram and paroxetine. Approximately one-third of patients had a history of different treatment strategies, such as antidepressant switching/combination therapy, for the improvement of clinical outcomes. The mean duration of aripiprazole augmentation was ~5 months; the mean time to the first increase of aripiprazole dose was almost 3 weeks; and the mean initial, first up-titrated, maximal, and maintenance doses of aripiprazole were 3.4, 4.2, 4.7, and 4.4 mg/day, respectively. The mean time to aripiprazole augmentation was approximately a month; more than half the patients received aripiprazole augmentation before 6 weeks after antidepressant treatment.

Table 1 Clinical parameters in the present study ($n=276$)

Clinical parameters	Values
Sex[b] (female)	192 (71.9)
Age (years)	39.0 (18.6)[a]
Antidepressants[b]	
Venlafaxine	119 (44.6)
Paroxetine	66 (24.7)
Escitalopram	82 (30.7)
Presence of past treatment strategies	92 (34.5)[b]
Prophylactic use of ADs	12 (4.5)[b]
ADs prescription during follow-up	32 (12.0)[b]
Time to increasing initial dose of aripiprazole (days)	19.1 (5.3)[a]
Discontinuation of aripiprazole after 3 months	124 (46.4)[b]
Duration of treatment (days)	138.0 (123.9)[a]
Initial dose (mg/day)	3.4 (1.5)[a]
First increased dose (mg/day)	4.2 (2.5)[a]
Maximal dose (mg/day)	4.7 (3.6)[a]
Maintaining dose (mg/day)	4.4 (3.5)[a]
Time to augmentation (days)	30.1 (10.2)[a]
Proportion of patient by add-on time[b] (days)	
0–21	72 (26.1)
22–42	76 (27.5)
After 42	128 (46.4)
Adverse events[b]	
Insomnia	57 (21.3)
Anxiety	42 (15.7)
Sedation	18 (6.7)
Headache	15 (5.6)
Palpitation	14 (5.2)
Weight gain	14 (5.2)
Fatigue	12 (4.5)
Dyspepsia (including nausea and vomiting)	12 (4.5)
Dizziness	7 (2.6)
Rigidity	7 (2.6)
Decreased appetite	6 (2.2)
Hyperphagia	6 (2.2)
Concentration difficulty	5 (2.2)
Dyspnea	4 (1.5)
Tremor, hand	4 (1.5)
Irritability	4 (1.5)

Data are represented as mean (SD)[a] or number (percent)[b] by the property of the variables.
ADs, antiparkinsonian drugs.

Interestingly, more than half the patients had been on aripiprazole augmentation without termination and only 10% of patients had been prescribed ADs during follow-up. The most frequent AEs were insomnia, followed by anxiety and sedation. Other frequent AEs included headache, palpitation, weight gain, fatigue, and dyspepsia. Possible extrapyramidal symptoms occurred in less than 5% of patients.

Discussion

The present findings suggest that the actual doses of aripiprazole augmentation used during routine clinical practice should be lower than those recommended by the

US FDA and a number of RCTs. The present dosing pattern analyses remind clinicians of the fact that the maximal benefit of certain medication could be gained by delicate optimal dosage, which could be obtained by several shared clinical experiences.

Although the majority of aripiprazole augmentation RCTs were not designed to identify the optimal dose for treating adult and elderly patients with MDD, the mean daily dose of aripiprazole in such studies ranged from 10 to 15 mg/day for acute and chronic treatment (Patkar *et al.*, 2006; Berman *et al.*, 2007, 2009, 2011; Marcus *et al.*, 2008; Nierenberg *et al.*, 2009; Pae *et al.*, 2007, 2011; Steffens *et al.*, 2011). In addition, patients achieved a terminal dose at week 3 and maintained this dose for the remainder of the registration RCTs (Berman *et al.*, 2007; Marcus *et al.*, 2008). It has been suggested that a starting dose of 2–5 mg/day with a target dose of 5–15 mg/day is prudent for patients with MDD (Nelson *et al.*, 2008; Nelson and Papakostas, 2009; Pae *et al.*, 2010, 2011).

In contrast, the starting, maximal, and maintenance doses of aripiprazole administered in the current study were considerably lower than those used in open-label and RCTs. In support of our findings, recent studies showing the beneficial effects of lower doses of aripiprazole augmentation for the treatment of MDD are increasing, particularly in Asian regions. For example, low-dose aripiprazole augmentation (2.5 mg/day) enhanced the efficacy of regular-dose sertraline in treatment-naive MDD patients (Lin *et al.*, 2011), indicating that aripiprazole augmentation may also be effective in the first-onset patients. The mean daily dose of aripiprazole augmentation (4.2 mg/day) in a Taiwanese study (Chen *et al.*, 2012) was quite similar to the doses used in our study. Of note, the population investigated in the Taiwanese study included refractory MDD patients, whereas the current patients were not treatment resistant. Findings from a western population study (Mischoulon *et al.*, 2012) using 5 mg/day of aripiprazole augmentation also show the modest additional benefits of aripiprazole augmentation treatment in patients who did not benefit from lower doses (2 mg/day). In addition, 2 mg/day of aripiprazole also showed marginal superiority over placebo in a recent RCT (Fava *et al.*, 2012). Intriguingly, low-dose aripiprazole augmentation (2–5 mg/day) resulted in a significant improvement only in the depression subscale of the Kellner Symptom Questionnaire compared with placebo augmentation, whereas such effects were not found on the anxiety, somatization, and hostility scales (Dording *et al.*, 2013). We cannot clearly determine whether differential efficacy between low (2–5 mg/day) and recommended doses (5–15 mg/day) of aripiprazole augmentation may exist at this point; hence, well-designed RCTs targeting establishment of a minimal effective dose as well as proving differential efficacy between such different doses are necessary.

In a recent large benefit claim-base study (Jing *et al.*, 2013) ($n = 8026$), the mean daily dose of aripiprazole augmentation decreased from 13.5 mg/day in 2006 to 6.9 mg/day in 2010, which also supports the present findings on low-dose aripiprazole augmentation use in routine practice. Finally, recent large open-label studies also support the use of low-dose aripiprazole augmentation (mean daily doses in both studies: $\sim$6 mg/day) in Korean patients (Jon *et al.*, 2013; Pae *et al.*, in press).

Because of the different genetic backgrounds of Asian and Western populations, ethnic differences must be considered when investigating the metabolism of antipsychotics (Yoon, 1995; Chong *et al.*, 1997; Shen *et al.*, 2007). Given the complex nature of the pharmacogenetic findings on MDD treatment, however, the clinical relevance of pharmacogenetics should be very limited today unless they consider all other clinical factors such as repeated history of treatment, number of episodes, the impact of life events, physician biases, or hidden differential metabolic capacities, which may be implied in pathophysiologies and management of MDD (Diaz and De Leon, 2002; Horstmann and Binder, 2009; Han and Pae, 2013). Currently, aripiprazole is approved as an augmentation therapy for the treatment of MDD in South Korea, Taiwan, Hong Kong, Thailand, the Philippines, and Indonesia and is pending approval in Japan in Asian Market. Thus, more data collected from routine practices in Asian and Western countries will help identify whether there should be actual differences in the prescription of aripiprazole for the treatment of MDD and may prompt the establishment of a minimal effective dose of aripiprazole augmentation for MDD.

This retrospective study has clear limitations. Each patient was followed from the index point for up to 1 year, but data collection was discontinued at this point, and any changes in aripiprazole dosage patterns after this point were not determined. In addition, dosing patterns over time according to symptom severity, clinical course of the patient, and antidepressant doses/types were not addressed. A much larger sample would be necessary to address these issues. This study was not designed prospectively; thus, the exact reasons for different aripiprazole augmentation initiation and titration patterns during the follow-up period could not be identified. The heterogeneity of the sample should also be considered. Our study was not prospectively intended to recruit partial or nonresponse patients; in fact, our sample may also include remitters with residual symptoms, minimal and partial responders, or nonresponders. When we reflect the existence of different situation of nation-based medical insurance and reimbursement systems across the world, the restriction of clinical use, different indication status by regulatory agency, and economic concerns of medication expenses by government control may also influence the dosing pattern of aripiprazole augmentation in a naturalistic

observational study. Finally, these data are based on information from only one university-based hospital and only on an outpatient basis; thus, we cannot generalize the present findings to all types of practice.

Conclusion

The current findings indicate that the actual doses of aripiprazole augmentation used in routine clinical practice may be on the lower end of the spectrum relative to US FDA recommendations and that the dosing patterns differ from those in RCTs. A number of clinical issues should be addressed in future well-designed and adequately powered clinical studies, including the minimal effective dose of aripiprazole augmentation, the appropriate timing of interventions, the adequate duration of augmentation, which agents should be discontinued after aripiprazole augmentation (antidepressant or aripiprazole), the subtype of depression for which aripiprazole augmentation is most effective, the best antidepressants for use with aripiprazole augmentation, and relapse rates after discontinuation of aripiprazole augmentation.

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Conflicts of interest

There are no conflicts of interest.

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