The effects of aripiprazole on the subscales of the Kellner Symptom Questionnaire in treatment resistant depression

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We have recently examined the efficacy of low-dose aripiprazole augmentation for major depressive disorder (MDD), with modest nonsignificant benefit found. In a secondary investigation, we examined whether aripiprazole resulted in improvement in four subscales (depression, anxiety, somatic symptoms, and hostility) of the Kellner Symptom Questionnaire (KSQ). We reanalyzed data from the main outcome study on 221 MDD patients with inadequate response to selective serotonin reuptake inhibitors or serotonin–norepinephrine reuptake inhibitors. Patients were randomized, using the sequential parallel comparison design, into two 30-day phases, as follows: drug/drug (aripiprazole 2 mg/day in phase 1, aripiprazole 5 mg/day in phase 2), placebo/drug (placebo in phase 1, aripiprazole 2 mg/day in phase 2), or placebo/placebo (placebo in both phases). We examined changes in the KSQ score from baseline to endpoint on the basis of the subscaled Well-being and Reversal Distressed Anxiety Subscales. The score for the KSQ depression subscale improved from baseline to the end of follow-up, with a significant advantage for aripiprazole over placebo ($P=0.0327$). Although improvement was also observed in the anxiety and hostility scales, neither attained a significant advantage over placebo; no significant change was observed for the somatization subscale. Aripiprazole augmentation resulted in a significant improvement compared with placebo augmentation only in the depression subscale of the KSQ; however, the low dose may not have been enough to have an impact on the anxiety and hostility scales. The good tolerability of the low dose may have resulted in the absence of worsening of somatic symptoms. Prospective studies are needed to better characterize the impact of low doses of aripiprazole augmentation on different manifestations of MDD. *Int Clin Psychopharmacol* 00:000–000 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Treatment resistant depression (TRD) presents a unique challenge in the clinical setting. TRD typically refers to nonresponse to standard antidepressant therapy (ADT) and occurs in about one-third of patients with major depressive disorder (MDD; Fava and Davidson, 1996). For patients who are refractory to traditional ADT, augmentation with another medication is often pursued. Several studies have shown that the use of atypical antipsychotic agents (AAP), such as aripiprazole, is an effective augmentation strategy to standard antidepressant treatments in TRD patients (Nelson and Papakostas, 2009). There are, however, many subtypes of depression such as anxious depression (Fava *et al.*, 1997), depression with anger attacks, and atypical depression, each characterized by a variety of different features (Fava *et al.*, 1997; American Psychiatric Association, 2000). It is reasonable to postulate that these subtypes, which have different symptoms, would respond to augmentation with an AAP in different ways. We therefore investigated the effects of aripiprazole on the following symptoms associated with MDD: depression, anxiety, hostility, and somatization.

Aripiprazole is an atypical antipsychotic with selectivity for multiple biogenic amine receptors. It is a partial agonist at D2 and D3 receptors, to which it binds with high affinity, whereas it has low affinity for all other dopamine receptors (Davies *et al.*, 2004). It is also a partial agonist at the 5HT1A receptor, as well as an antagonist at the 5HT2A receptor. This mechanism of action gives aripiprazole a unique profile as an antipsychotic, which supports the numerous investigations on its use across a wide range of psychiatric diseases.

Previous studies using aripiprazole as an adjunctive treatment have shown that it is effective in treating TRD (Nelson and Papakostas, 2009). Patients with minimal response to ADT experienced rapid clinical improvement with the addition of aripiprazole (2–20 mg) to their ADT (Thase *et al.*, 2008; Nelson *et al.*, 2012). These patients showed marked improvement compared with those receiving adjunctive placebo. In another study,

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patients receiving between 2 and 15 mg of adjunctive aripiprazole showed significantly greater improvement in their depressive symptoms compared with patients receiving adjunctive placebo (Berman *et al.*, 2007).

Recently, there has been a growing interest in the use of aripiprazole in the treatment of anxiety disorders, particularly in patients who are resistant to standard ADT with a selective serotonin reuptake inhibitor (SSRI). Like MDD, generalized anxiety disorder (GAD) is a chronic disorder, and full remission is achieved in only 25% of the patients (Yonkers *et al.*, 1996). With growing evidence for the involvement of dopamine as a neuromodulator in the development of fear conditioning, a few studies have examined the role of aripiprazole as a potential adjunct in standard SSRI therapy for GAD (Pezze and Feldon, 2004). Worthington *et al.* (2005) and Hoge *et al.* (2008) found significant global improvements in patients with resistant GAD treated with adjunctive aripiprazole therapy, and Menza *et al.* (2007) found a reduction in anxiety symptoms as well as the secondary outcome of improvement in depressive symptoms. Atypical antipsychotics have been used off-label to augment SSRI therapy for obsessive–compulsive disorder (OCD), and two recent small studies have indicated that aripiprazole is effective for this indication (Matsunaga *et al.*, 2011; Higuma *et al.*, 2012).

In addition to depressive symptoms, many patients with MDD also experience hostility, irritability, and/or aggression. Although the effects of aripiprazole on hostility in depression have not been specifically examined, aripiprazole has been shown to decrease hostility in a number of other disorders such as borderline personality disorder (Nickel *et al.*, 2006), schizophrenia (Robb *et al.*, 2010), and bipolar disorder (Frye, *et al.*, 2008). Intramuscular aripiprazole decreased agitation in bipolar and schizophrenic patients (Currier *et al.*, 2007) and was found to lead to significantly less sedation compared with lorazepam when used for this purpose (Zimbroff *et al.*, 2007).

Finally, there are no published studies specifically examining aripiprazole in the treatment of somatic manifestations of psychiatric disorders. However, there is much information on physical side effects of aripiprazole, some of which may manifest as somatic symptoms. All the antipsychotic agents have the potential for side effects, mediated by their interactions with dopaminergic, histaminergic, serotonergic, or adrenergic receptors. Aripiprazole, in comparison with several other atypical antipsychotics, has been associated with higher rates of stiffness and tremor and overall sensitivity (Edwards and Smith, 2009).

In the current study, an ancillary investigation of a large-scale randomized clinical trial on aripiprazole augmentation in TRD (Fava *et al.*, 2012), we examined aripiprazole's efficacy using the Kellner Symptom Questionnaire (KSQ), a 96-item, self-rated scale widely used in clinical trials of psychotropic drugs, in detecting changes in the overall well-being across a variety of scales (Kellner and Sheffield, 1967; Kellner, 1987; Zeffert *et al.*, 1996). Given the variety of uses of aripiprazole under investigation, such a measure seemed practical because it examines symptomatology across the four major domains of MDD, specifically depression, anxiety, hostility, and somatization. On the basis of the existing evidence and the unique pharmacologic profile of aripiprazole, we hypothesized that aripiprazole would reduce symptoms of depression, anxiety, and hostility, but might, through drug-induced adverse effects, increase somatic symptoms, which would be reflected in the somatization subscale.

Methods

We carried out a secondary analysis based on a sample from a parent study by (Fava *et al.*, 2012). In brief, this study was a 60-day, double-blind, placebo-controlled study on the efficacy of low-dose aripiprazole augmentation of antidepressant therapy (ADT) in MDD patients with inadequate response to SSRIs or selective serotonin–norepinephrine reuptake inhibitors. This study was conducted with the approval of the Partners Human Research IRB in accordance with the Declaration of Helsinki. In total, 221 MDD patients with inadequate response to ADT were recruited from eight academic and 14 nonacademic sites throughout the USA. Participants in the study were screened over 14–28 days, with MDD being diagnosed using the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Axis I Disorders – Patient Edition (First *et al.*, 1995). The validity of participants' major depressive episode was determined using the SAFER criteria interview (Targum *et al.*, 2008), administered remotely by telephone to patients previously deemed eligible after preliminary screening at the respective participating clinical sites. The SAFER interviews were conducted by Massachusetts General Hospital psychiatrists and psychologists trained in the use of this instrument.

The following patients were included: (i) men and women, aged between 18 and 65 years, able to provide informed consent and report for regularly scheduled office visits. (ii) Patients with a score of greater than 15 on the Quick Inventory of Depressive Symptomatology, self-rated version (Rush *et al.*, 2013), at screening and baseline visits. (iii) Patients treated with an adequate dose of SSRIs or serotonin–norepinephrine reuptake inhibitors during the current episode for at least 8 weeks, with the same, adequate dose over the last 4 weeks and for the duration of the study. (iv) Patients with a history of one, two, or three inadequate responses to adequate antidepressant trials (including the current trial) during the current major depressive episode, defined as a less than 50% reduction in the severity of depressive symptoms. This was determined using the MGH Antidepressant Treatment

Response Questionnaire (ATRQ), administered remotely by telephone during the SAFER interview. An adequate ADT trial was defined as treatment with at least a minimum dose of antidepressant treatment per the ATRQ for at least 6 weeks. (v) Patients scoring 18 or more on the 17-item Hamilton Depression Scale at the end of the screening phase. This was administered by study clinicians at the end of the screening phase and at baseline visits, as well as remotely by independent raters during the screening phase.

The sequential parallel comparison design (SPCD) method (Fava *et al.*, 2003) was used to divide the trial into two 30-day phases. Participants were randomized to 2 mg/day aripiprazole or placebo and were assigned, in a 2 : 3 : 3 ratio, to one of three sequence arms: drug/drug (aripiprazole 2 mg/day in phase 1, aripiprazole 5 mg/day in phase 2), placebo/drug (placebo in phase 1, aripiprazole 2 mg/day in phase 2), or placebo/placebo (placebo in both phases). All participants continued on their stable ADT doses, with no dose adjustments allowed during the randomization phase.

As a secondary measure in the parent study, and the main outcome measure in this ancillary investigation, the KSQ (Kellner, 1987) was administered at every study visit, including screening and baseline visits, to assess improvement in well-being. This measure is a self-reported, 92-item (yes/no) questionnaire that assesses distress and well-being across four domains: depression, anxiety, somatization, and hostility. These scales have been shown to be valid and reliable in detecting differences between psychotropic drugs and placebo in clinical trials and in eliciting differences in levels of distress between groups. Briefly, the principal scales of KSQ comprise matching distress (depressive, anxiety, somatic, or hostility–irritability symptoms, scored 0–17) and well-being (contentment, relaxation, physical well-being, or friendliness, scored 0–6) subscales that are scored in opposite directions – that is, affirmative responses to the distress items are scored positively, whereas affirmative responses to the well-being scales are scored negatively. The scores are then combined for each of the principal categories; thus, a higher combined score reflects higher distress levels and lower well-being levels within that category.

In the main outcome report (Fava, *et al.*, 2012), findings were presented for the entire KSQ score. In this related investigation, we examined the four individual subsections of the KSQ: depression, anxiety, hostility, and somatization. The main question was whether there was significant improvement in these subsection scores with the two regimens of Abilify (2 and 5 mg; Otsuka America Pharmaceutical Inc., Rockville, Maryland, USA).

A generalized estimating equations model (SAS Proc Genmod) was implemented to analyze the observed case changes in the KSQ, with baseline scores, treatment, and phase 1 baseline symptom severity as covariates, using an approach analogous to that applied for the change of MADRS scores in the main outcome paper (Fava *et al.*, 2012). Treatment effect was based on appropriate contrasts, with equal weights given to each phase and adjustment for study center only if it was retained in the final model of the primary analysis.

For these analyses, we examined changes in the KSQ score from baseline to endpoint on the basis subscaled Well-being and Reversal Distressed Anxiety Subscales. The latter refers to the fact that when the scales are added to form the combined scale scores, the well-being score is subtracted from 6, so as to focus on 'pathological' symptoms.

Results

KSQ scores for anxiety, depression, somatization, and anger–hostility are summarized in Tables 1–4, respectively. The change in the KSQ score for the depression subscale improved from baseline to the end of follow-up, with a significant advantage for aripiprazole over placebo ($P = 0.0327$). Although improvement was also observed in the other three subscales, none demonstrated a significant difference between aripiprazole and placebo.

Discussion

Aripiprazole has documented efficacy as augmentation therapy in MDD (Berman *et al.*, 2007; Thase *et al.*, 2008; Nelson and Papakostas, 2009; Nelson *et al.*, 2012) and anxiety disorders (Pezze and Feldon, 2004; Worthington *et al.*, 2005), as well as effectiveness in treating hostility and aggression in a variety of psychiatric disorders (Nickel *et al.*, 2006). On the basis of these previous studies, we hypothesized that when examining subscales of KSQ, we would find improvement in mood and anxiety, as well as anger–hostility, subscores. However, aripiprazole augmentation resulted in a significant improvement compared with placebo augmentation only in the depression subscale of KSQ.

Studies that have documented the efficacy of aripiprazole in the treatment of agitation have used higher doses, ranging from 9.75 to 15 mg/day (Zimbroff *et al.*, 2007), 10 to 30 mg/day (Robb *et al.*, 2010), and 15 mg/day (Nickel *et al.*, 2006). Similar doses were found to be effective for anxiety symptoms. In patients with GAD, doses starting at 10 mg/day (Menza *et al.*, 2007) were effective and in patients with depression and comorbid anxiety, doses ranging from 15 to 30 mg/day were effective (Worthington *et al.*, 2005). By comparison, our doses were much lower than those used in these studies, and this difference could have resulted in failure to show a significant difference compared with placebo in some of the KSQ outcome measures. Indeed, the parent study did not find a significant advantage for aripiprazole over placebo at

Table 1 Comparison of change in the KSQ score based on the subscaled Well-being and Reversal Distress Anxiety Subscale from baseline to the end of follow-up between treatment groups, primary efficacy sample, and observed case analysis

	Drug		Placebo			
Measure	Phase I	Phase II	Phase I	Phase II	Weighted difference (95% CI)	*P*-value*
Baseline KSQ score						
Mean±SD (*N*)	13.98±5.23 (54)	12.98±5.38 (61)	14.91±4.67 (167)	12.98±4.47 (63)	−0.33 [−1.33, 0.68]	
Range (min, max)	(4.00, 22.00)	(2.00, 23.00)	(4.00, 23.00)	(1.00, 22.00)		
Median	15.00	13.00	16.00	13.00		
Follow-up KSQ score						
Mean±SD (*N*)	10.33±5.33 (52)	10.51±6.41 (59)	11.62±5.77 (162)	10.90±5.95 (61)	−0.89 [−2.17, 0.39]	
Range (min, max)	(0.00, 22.00)	(0.00, 23.00)	(0.00, 23.00)	(0.00, 23.00)		
Median	10.00	12.00	12.00	10.00		
Mean change in KSQ scores from baseline						
Mean±SD (*N*)	−3.62±4.77 (52)	−2.66±6.14 (59)	−3.23±4.87 (162)	−2.08±4.58 (61)	−0.55 [−1.70,0.60]	0.3445
Range (min, max)	(−16.00, 4.00)	(−21.00, 12.00)	(−17.00, 10.00)	(−17.00, 9.00)		
Median	−3.00	−2.00	−3.00	−1.00		

CI, confidence interval; KSQ, Kellner Symptom Questionnaire.
**P*-value was generated using generalized estimating equations.

Table 2 Comparison of change in the KSQ score based on the subscaled Well-being and Reversal Distress Depression Subscale from baseline to the end of follow-up between treatment groups, primary efficacy sample, and observed case analysis

	Drug		Placebo			
Measure	Phase I	Phase II	Phase I	Phase II	Weighted difference (95% CI)	*P*-value*
Baseline KSQ score						
Mean±SD (*N*)	17.11±4.47 (54)	15.33±5.06 (61)	18.10±4.08 (167)	15.84±5.22 (63)	−0.68 [−1.68,0.32]	
Range (min, max)	(5.00, 23.00)	(3.00, 23.00)	(4.00, 23.00)	(2.00, 23.00)		
Median	19.00	15.00	19.00	17.00		
Follow-up KSQ score						
Mean±SD (*N*)	11.96±6.38 (52)	11.54±7.01 (59)	13.74±6.55 (162)	13.49±6.65 (61)	−1.79 [−3.26, −0.33]	
Range (min, max)	(1.00, 21.00)	(0.00, 23.00)	(0.00, 23.00)	(0.00, 23.00)		
Median	12.50	13.00	15.00	15.00		
Mean change of KSQ scores from baseline						
Mean±SD (*N*)	−5.23±5.12 (52)	−3.80±6.63 (59)	−4.31±6.12 (162)	−2.15±4.99 (61)	−1.44 [−2.76, −0.12]	0.0327
Range (min, max)	(−18.00, 5.00)	(−20.00, 7.00)	(−20.00, 9.00)	(−16.00, 9.00)		
Median	−4.00	−2.00	−3.00	−1.00		

CI, confidence interval; KSQ, Kellner Symptom Questionnaire.
**P*-value was generated using generalized estimating equations.

Table 3 Comparison of change in the KSQ score based on the subscaled Well-being and Reversal Distress Somatic Subscale from baseline to the end of follow-up between treatment groups, primary efficacy sample, and observed case analysis

	Drug		Placebo			
Measure	Phase I	Phase II	Phase I	Phase II	Weighted difference (95% CI)	*P*-value*
Baseline KSQ score						
Mean±SD (*N*)	11.09±5.23 (54)	10.84±5.42 (61)	12.05±5.47 (167)	10.21±5.68 (63)	0.33 [−0.71,1.37]	
Range (min, max)	(1.00, 20.00)	(2.00, 23.00)	(0.00, 23.00)	(0.00, 22.00)		
Median	12.00	11.00	12.00	10.00		
Follow-up KSQ score						
Mean±SD (*N*)	9.56±5.56 (52)	10.15±5.47 (59)	10.12±5.83 (162)	9.70±5.80 (61)	−0.41 [−1.46,0.64]	
Range (min, max)	(0.00, 23.00)	(0.00, 23.00)	(0.00, 23.00)	(0.00, 20.00)		
Median	9.50	10.00	10.00	10.00		
Mean change in KSQ scores from baseline						
Mean±SD (*N*)	−1.42±3.90 (52)	−0.83±3.43 (59)	−1.94±4.33 (162)	−0.41±3.35 (61)	0.11 [−0.74,0.96]	0.7977
Range (min, max)	(−10.00, 8.00)	(−11.00, 9.00)	(−15.00, 9.00)	(−13.00, 12.00)		
Median	−1.00	0.00	−2.00	0.00		

CI, confidence interval; KSQ, Kellner Symptom Questionnaire.
**P*-value was generated using generalized estimating equations.

doses of 2 or 5 mg/day (Fava *et al.*, 2012; Mischoulon *et al.*, 2012). The fact that the KSQ score for the subscale of depression was statistically superior compared with that for placebo in this study may reflect a general improvement in depressive symptoms observed in the parent study, which did not reach statistical significance (Fava *et al.*, 2012).

Although aripiprazole results in a lower incidence of many of the adverse events commonly experienced by patients

Table 4 Comparison of change in the KSQ score based on the subscaled Well-being and Reversal Distress Anger–Hostility Subscale from baseline to the end of follow-up between treatment groups, primary efficacy sample, and observed case analysis

	Drug		Placebo			
Measure	Phase I	Phase II	Phase I	Phase II	Weighted difference (95% CI)	*P*-value*
Baseline KSQ score						
Mean±SD (*N*)	10.81±6.26 (54)	10.00±6.41 (61)	11.91±6.05 (167)	9.83±6.44 (63)	−0.45 [−1.74,0.85]	
Range (min, max)	(0.00, 22.00)	(0.00, 23.00)	(0.00, 23.00)	(0.00, 23.00)		
Median	11.00	9.00	11.00	9.00		
Follow-up KSQ score						
Mean±SD (*N*)	7.96±5.89 (52)	6.97±6.22 (59)	8.88±6.64 (162)	7.89±5.25 (61)	−0.93 [−2.12,0.25]	
Range (min, max)	(0.00, 22.00)	(0.00, 23.00)	(0.00, 23.00)	(0.00, 23.00)		
Median	7.00	6.00	7.00	8.00		
Mean change in KSQ scores from baseline						
Mean±SD (*N*)	−2.88±5.11 (52)	−2.83±5.04 (59)	−2.96±5.97 (162)	−1.87±4.73 (61)	−0.58 [−1.61,0.45]	0.2669
Range (min, max)	(−15.00, 10.00)	(−19.00, 6.00)	(−22.00, 17.00)	(−18.00, 13.00)		
Median	−2.50	−1.00	−2.00	−1.00		

CI, confidence interval; KSQ, Kellner Symptom Questionnaire.
**P*-value was generated using generalized estimating equations.

on other AAPs, including sleepiness, nausea, dry mouth, and increased appetite (Stroup *et al.*, 2011), it is more likely than risperidone, olanzapine, quetiapine, or ziprasidone to cause other physical effects, such as stiffness or tremor (Edwards and Smith, 2009). Thus in those patients who tend to somatize, an agent that is more likely to cause neuromuscular symptoms such as stiffness or tremor may obscure any improvement in somatization symptoms of MDD that typically parallels improvement in depressive symptoms. Our findings, however, did not suggest any significant worsening of somatic symptoms in the aripiprazole augmentation group compared with placebo and may be a reflection of the generally good tolerability of the lower doses of aripiprazole (Fava *et al.*, 2012; Mischoulon *et al.*, 2012).

Our investigation is limited by the small dose range of the study medication, aripiprazole, as well as by the retrospective nature of the analysis. It is possible that higher doses of aripiprazole, more consistent with those used in the original pivotal studies, may have resulted in a more robust improvement in the KSQ subscales, as well as worsening of somatic symptoms. Prospective studies are needed to better characterize the impact of low doses of aripiprazole augmentation on different manifestations of MDD.

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Conflicts of interest

Dr Dording has received Research Support from Abbott Laboratories, Alkermes, Aspect Medical Systems, AstraZeneca, Bristol-Myers Squibb Company, Cephalon, Eli Lilly & Company, Forest Pharmaceuticals Inc., GlaxoSmithkline, J & J Pharmaceuticals, Lichtwer Pharma GmbH, Lorex Pharmaceuticals, Novartis, Organon Inc., PamLab, LLC, Pfizer Inc., Pharmavite, Roche, Sanofi-Aventis, Solvay Pharmaceuticals Inc., Synthelabo, and Wyeth-Ayerst Laboratories. Dr Dording has served as an advisor/consultant for Takeda. Dr Dording has been a speaker for Wyeth-Ayerst Laboratories. Dr Pencina has received a consulting fee/honoraria from BMS. He has also been a consultant for PamLab and RTC Logic and has a grant from the NIMH. Dr Fava serves on the boards for Eisai, *En Vivo*, GenOmind, Psylin, Scherring Plough, and BMS, Otsuka. He has consulted for Abbott Laboratories, Affectis Pharmaceuticals AG, Alkermes Inc., Amarin Pharma Inc., Aspect Medical Systems, Astra-Zeneca, Auspex Pharmaceuticals, Bayer AG, Best Practice Project Management Inc., BioMarin Pharmaceuticals Inc., Biovail Corporation, BrainCells Inc., Bristol-Myers Squibb, CeNeRx BioPharma, Cephalon Inc., Clinical Trials Solutions, LLC, CNS Response Inc., Compellis Pharmaceuticals, Cypress Pharmaceutical Inc., DiagnoSearch Life Sciences (P) Ltd, Dinippon Sumitomo Pharma Co. Inc., Dov Pharmaceuticals Inc., Edgemont Pharmaceuticals, Inc., Eisai Inc., Eli Lilly and Company, *En Vivo* Pharmaceuticals Inc., ePharma-Solutions, EPIX Pharmaceuticals Inc., Euthymics Bioscience Inc., Fabre-Kramer Pharmaceuticals Inc., Forest Pharmaceuticals Inc., GenOmind, LLC, GlaxoSmithKline, Grunenthal GmbH, i3 Innovus/Ingenis, Janssen Pharmaceutica, Jazz Pharmaceuticals Inc., Johnson & Johnson Pharmaceutical Research & Development, LLC, Knoll Pharmaceuticals Corp., Labopharm Inc., Lorex

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