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Aripiprazole augmentation strategy in clomipramine-resistant depressive patients: An open preliminary study

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Abstract

Recent evidence supports the use of second generation antipsychotics in drug resistant depression. The aim of the present open-label study was to evaluate the effect of aripiprazole as an add-on medication in drug-resistant depressed patients who had not responded to clomipramine. Thirty-five patients with major depressive disorder (MDD) were included in the study. All patients had not responded to a previous adequate treatment with an SSRI and had been receiving clomipramine (daily doses ranging from 100 to 300 mg) for 113.9±18.9 days without getting significant clinical improvement. Aripiprazole was added at the fixed dose of 5 mg/day and clinical status as well as clomipramine plasma levels were monitored before and after 4, 8, and 24 weeks of combined treatment. Hamilton depression rating scale scores significantly decreased over the follow-up period with 91.4% and 34.3% of patients getting a response or a remission, respectively, after 24 weeks of combined treatment. No worsening of clomipramine-related side effects nor new side effects were observed. The clinical improvement was accompanied by a progressive and significant increase in clomipramine plasma levels. With the limitation of an open-label design, these data suggest for the first time the putative efficacy and safety of aripiprazole in combination with a tricyclic medication in drug resistant depressed patients. The role of the observed pharmacokinetic interaction in the mechanism of aripiprazole antidepressant activity remains to be proved.

1. Introduction

In spite of the availability and use of antidepressant drugs, the number of depressive patients who do not obtain a

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response from therapy is considerable (Rush et al., 2006a; Fava, 2003); only 60–70% of affected patients respond to treatment for major depressive disorder (MMD) (Trivedi et al., 2004).

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) project reported that remission rate with a first adequate trial of an antidepressant is typically only about 30% in a naturalistic setting (Rush et al., 2006b), suggesting that more than two third of depressed patients will need alternative or adjunctive treatment. Moreover, several studies indicate that a percentage between 20 and 46% of depressed patients show no or partial response to antidepressant treatment (Trivedi et al., 2006; Ananth, 1998) and residual symptoms are very common (Cuffel et al., 2003). This condition is of particular concern, since patients with residual symptoms have greater risk of relapse/recurrence and a worse social functioning than patients who achieve remission (Yang et al., 2010).

The term "resistant depression" refers to a clinical picture of depression in which there is no response to two antidepressant drugs with different mechanism of action, each of one used in adequate dosage and for a sufficient period of time (Ananth, 1998). Recently, Thase and Rush (1997) have proposed a multi-staging method for resistant depression ranging from stage 0 (no adequate antidepressant trial) to stage 4 (no response to 4 or more adequate antidepressant trial). From a pharmacological point of view, possible strategies to manage treatment-resistant patients include the use of different antidepressant drugs (switching), the concomitant use of another antidepressant molecule (combination therapy) or the addition of non-antidepressants such as lithium, thyroid hormones or antipsychotics (augmentation therapy). A recent meta-analysis (Papakostas et al., 2007) suggests that augmentation of an antidepressant with second generation antipsychotic such as olanzapine, risperidone or quietapine may have some benefits in antidepressant-resistant forms of depression. The STAR*D project also demonstrated that there were no differences in remission rates or times to remission among medication switch or medication augmentation strategies at any treatment level (Rush et al., 2006a, 2006b; Trivedi et al., 2006).

Although the STAR*D project has not been applied to evaluate the use of atypical antipsychotics for antidepressant treatment-resistant major depressive disorders, there are some data supporting efficacy for atypical antipsychotic augmentation of antidepressants in patients who do not fully respond to antidepressant monotherapy (Shelton and Papakostas, 2008).

Aripiprazole, an atypical antipsychotic, seems to be a promising drug due to its peculiar mechanism of action. The partial agonism at the D_2 and D_3 receptors and at the 5-HT_{1A} receptor, coupled with antagonism at the 5-HT_{2A} receptors, can contribute to its antidepressant effect as an adjunctive drug in treatment-resistant depressed patients (Rutherford et al., 2007; Shapiro et al., 2003; Jordan et al., 2004). Indeed, open-label and randomized controlled trial (Pae et al., 2008) studies support the use of aripiprazole as an adjunctive agent in patients with MDD who did not respond to previous non-tryciclic antidepressant drugs (Weber et al., 2008). In fact aripiprazole in combination with different SSRIs or venlafaxine or mirtazapine was proved to be a useful add-on agent for depressed patient who had not responded to those molecules (Pae et al., 2007; Marcus et al., 2008; Sheffrin et al., 2009).

The role of aripiprazole as adjunctive drug in tryciclic non responder patients has never been reported, although there have been two reports of aripiprazole successful augmentation in clomipramine-treated obsessive-compulsive disorder patients (da Rocha and Correa, 2007; Friedman et al., 2007).

The aim of the present study, thereby, was to evaluate the possible efficacy of aripiprazole in adjunction to clomipramine in depressed patients who had not responded to the tricyclic alone and to a previous treatment with a non-tryciclic drug. Furthermore, plasma levels of clomipramine were measured in basal condition and after the combination with aripiprazole, in order to highlight possible pharmacokinetic interactions.

2. Experimental procedures

This is a prospective, open-label study that was carried out in patients consecutively recruited at the Department of Psychiatry of the University of Naples. A patient was included in the study if he/she met the following criteria: 1) age between 18 and 65 years; 2) a DSM-IV diagnosis of recurrent MDD, confirmed by the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 1997); 3) a duration of illness of at least 2 years; 4) no history of past or current drug abuse or dependence; 5) absence of any neurological or physical illness requiring a specific treatment; 6) history of no response to a previous adequate trial with a Selective Serotonin Reuptake Inhibitor (SSRI) at the manufacturer-recommended daily dose for at least 6 weeks, and no response to a current adequate trial with clomipramine at the daily dose of at least 100 mg/day for 6 weeks; 7) willingness to participate in the study, expressed by providing written informed consent after complete description of the protocol. The study was approved by our institutional review board.

At baseline, each recruited patient was clinically assessed by the administration of the 21-item Hamilton rating scale for depression (HDRS) (Hamilton, 1960) and the SCID-I. Patients' sociodemographic characteristics (age and sex) and clinical variables (age at onset and duration of the illness, number of previous hospitalizations) were recorded by an ad-hoc anamnestic form that is commonly used in our department.

Thirty-five patients (14 males and 21 females), with a mean age at intake of 38.77 (SD = 11.51) were enrolled.

At the study entry, patients were receiving clomipramine without getting any clinical response and had not responded to a previous adequate treatment with citalopram (3/35 patients, 8.6%), escitalopram (1/35, 3%), fluoxetine (2/35, 5.7%), fluvoxamine (8/35, 22.8%), paroxetine (10/35, 28.5%), and sertraline (11/35, 31.4%). Therefore their treatment resistant depression fulfilled the stage 2 criteria of Thase and Rush's classification (Thase and Rush, 1997). The diagnosis of MDD and the clinical assessments were made by a senior psychiatrist (M.F.) who had received a formal training in the use of the assessment instruments and had a long experience in the application of these instruments in research settings.

Following the initial assessment, all clomipramine-treated-patients, received a fixed dose of 5 mg/day of aripiprazole in adjunction. The dose of clomipramine remained unchanged during the study unless subject noted intolerable newly emergent antidepressant-related side effects. Patients were rated on the HDRS before and 4, 8 and 24 weeks after starting aripiprazole. Response to treatment was defined as a decrease of at least 50% of the HDRS total score at the beginning of the combined treatment. Remission was defined as a HDRS total score ≤ 7. Side effects were assessed at the same time points by a non-structural clinical interview.