Aripiprazole high-dose: off-label use in schizophrenia

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Despite the lack of evidence, use of higher than recommended antipsychotic doses is common in refractory patients with schizophrenia [1, 2]. The Royal College of Psychiatrists (United Kingdom) defines high-dose antipsychotic therapy as "a total daily dose of a single antipsychotic which exceeds the upper limit stated in the Summary of Product Characteristics (SPC) or British National Formulary (BNF) with respect to the age of the patient and the indication being treated..." [1]. In clinical practice, aripiprazole is one of the second-generation antipsychotics most used at high dose [2]. Several case reports of aripiprazole at high dose (>30 mg/d) have been published showing mixed results about efficacy and safety (table 1) [3–7]. A double blind randomised controlled trial (RCT) evaluated safety and efficacy of intramuscular injection of aripiprazole lauroxil 441 mg (300-mg aripiprazole equivalent), aripiprazole lauroxil 882 mg (600-mg aripiprazole equivalent) or placebo in 623 patients with acute exacerbation of symptoms of schizophrenia. Neither aripiprazole dose showed clinically significant differences in efficacy and safety [8] although a post hoc analysis of this study found that the higher dose was more effective in patients with more severe illness [9]. Another double-blind RCT study investigated efficacy and safety of different dosages of aripiprazole including overdoses. Forty patients with stable schizophrenia spectrum disorders, randomised to aripiprazole 30 mg/d, 45 mg/d, 60 mg/d, 75 mg/d or 90 mg/d for more than 15 days did not show clinically significant differences in efficacy and safety [10]. In line with this study, an analysis performed on efficacy data from five short term RCTs (n = 1605) showed that doses above 20 mg/d did not provide additional benefit or even reduce efficacy [11]. In contrast, a study evaluating aripiprazole serum levels for 283 patients under steady-state conditions showed concentration-related side effects [12]. Aripiprazole is an atypical antipsychotic characterized by a 5-hydroxytryptamine (5-HT)1A agonism, 5-HT2A antagonism and a partial agonism, low dissociation kinetics and high binding affinity towards dopamine D2/D3 receptors [13]. A dose of 30 mg/d induces a D2/D3 receptor occupancy of almost 95%, therefore additional doses exert mainly a greater effect on serotonin/histamine/adrenergic transmission [14]. Results from a naturalistic study suggest that high-dose first-generation antipsychotics may be beneficial in subpopulations [15]. With antipsychotic overdose, one of the major concerns is the frequency of dose-dependent QTc prolongation and extra pyramidal symptoms (EPS) [12, 16]. The low frequency of EPS with high doses, mediated by D2 partial agonism / 5-HT2 receptor antagonism [6, 13, 17], and the capability to reduce QTc interval [18] make it a safer antipsychotic choice if high dosages are necessary. Differences in absorption, CYP 450 metabolism, penetration across the blood-brain barrier may explain the extensive human pharmacokinetic variability of aripiprazole and subtherapeutic drug plasma levels at a standard dose [2]. Although some patients experience increased benefit from receiving high-dose antipsychotics, the current evidence does not support this pharmacological strategy in resistant schizophrenia. Switching medication or clozapine (after failure of adequate trials with two different antipsychotics) should be preferred [1].

Table 1: Summary of five case reports with high-dose aripiprazole in schizophrenia.

Source	Age and diagnosis	Aripiprazole dosage	Time (weeks)	Outcome
Chavez and Poveda 2006 [3]	57-year-old patient with schizophrenia	60 mg/d	28	No worsening of symptoms. No adverse effects
Duggal and Mendhekar 2006 [4]	21-year-old patient with schizophrenia	75 mg/d	4	Improvement in psychotic symptoms. No adverse effect except sinus tachycardia
Thone 2007 [5]	31-year-old patient with schizophrenia	60 mg/d	Not available	No improvement in psychotic symptoms. Safety data not reported
Wichowicz et al. 2012 [6]	30-year-old patient with schizophrenia	105 mg/d	2	No improvement in psychotic symptoms. No adverse effect except mild EPS and akathisia
Bartova et al. 2015 [7]	72-year-old patient with schizophrenia	1200 mg/4 weeks (long-acting formulation)	12	Improvement in psychotic symptoms. No adverse effects

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References
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