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Brief articles

Aripiprazole and Risperidone for Treatment of Methamphetamine-Associated Psychosis in Chinese Patients

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ABSTRACT

We evaluated tolerability and efficacy of aripiprazole and risperidone for treatment of methamphetamine (METH) associated psychotic symptoms in China. Patients with acute METH-associated psychotic symptoms (N = 42) and with Positive and Negative Syndrome Scale (PANSS) total score between 60 and 120 were randomized to aripiprazole (initial dose 5–10 mg per day followed by flexible doses 5–15 mg per day) or risperidone (initial dose 2–4 mg per day followed by flexible doses 4–6 mg per day) from day 3 to 25 of inpatient hospital stay. Outcome measures included PANSS and Clinical Global Impressions-Severity of Illness scale (CGI-S), METH craving Visual Analogue Scale (VAS), Simpson Angus Scale (SAS), Barnes Assessments Akathasia Rating Scale (BARS), and self-reported adverse effects evaluated during treatment. Retention was evaluated using Kaplan-Meier survival analysis and the MIXED models procedure was used to compare the groups on measures of psychotic and extra-pyramidal symptoms. Patients in both aripiprazole and risperidone groups showed statistically significant reductions in psychotic symptomatology from baseline during treatment ($p < 0.001$) with no statistically significant differences between the treatment groups ($p = 0.73$ and $p = 0.15$, respectively). Risperidone-treated patients reported significantly greater METH craving reductions ($p < 0.001$). Overall, 71% of patients completed the entire study, but the aripiprazole group had a significantly lower retention than the risperidone group ($p = 0.007$), primarily due to medication related adverse effects. Aripiprazole-treated patients also had significantly more akathisia ($p = 0.03$) and agitation ($p = 0.02$) than risperidone-treated patients. Patients in both groups who tolerated their medications and completed the entire study achieved comparable reductions of psychotic symptoms.

1. Introduction

Amphetamine type stimulants (ATS) have become commonly consumed illicit substances: between 0.3 and 1.3% of the world's population uses ATS and methamphetamine (METH) use is highly prevalent in East and South-East Asia (UNDOC, 2012). The number of registered ATS users increased dramatically in recent years in China from 0.36 million (27% of all registered drug users) in 2010 to 1.08 million (43.8% of all registered drug users) in 2014, and METH use is reported by about 78% of registered ATS users in China (CNNCC, 2010-2014). The recent dramatic increase in use of ATS including METH, in China and throughout Asia has also brought substantial problems with both acute and persistent psychosis associated with ATS use. The reported prevalence of psychosis in METH users ranges between 10% and 60% (Farrell, Marsden, Ali, & Ling, 2002; Mahoney, Kalechstein, De La Garza, & Newton, 2008; McKetin, McLaren, Lubman, & Hides, 2006). To address these problems, special hospitals or hospital units have been established in China to treat patients with persistent psychosis associated with ATS use (Ding, Lin, Zhou, Yan, & He, 2014; Tang, Cheung, Liang, Ungvari, & Tang, 2011; Zhang et al., 2013, 2014). However, treatment of psychosis in these patients is complicated by the dearth of evidence-based clinical protocols or established efficacious pharmacological treatments.

Research and clinical evidence supports the use of several classes of medications, including conventional antipsychotics, newer antipsychotics, and benzodiazepines for treating METH-related psychotic symptoms in inpatient settings (Shoptaw, Kao, & Ling, 2009). Atypical antipsychotic medications, including aripiprazole, a partial agonist at the dopamine (DA) and serotonin (5-HT) receptor, and risperidone, an antagonist at both DA and 5-HT receptors, have also demonstrated safety and limited efficacy for treatment of METH-associated psychosis (Meredith, Jaffe, Yanasak, Cherrier, & Saxon, 2007; Misra & Kofoed, 1997; Sulaiman et al., 2012, 2013) are frequently used as the first-line treatment in clinical practice in China. It has, however, been observed and reported in both published (Wang, Devi Thakoor, Wang, & Hao, 2014) and unpublished communications from doctors in China that

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administration of aripiprazole for treatment of METH-associated psychosis results in frequent side effects including restless and irritability, and the safety and tolerability of both aripiprazole and risperidone for treatment of METH-associated psychosis have not been comprehensively evaluated in China or elsewhere. Consequently, this study compared the safety, tolerability and efficacy of aripiprazole and risperidone for treatment of METH-associated psychosis, in typical clinical settings and using dosages and regimens commonly employed in clinical practice in China.

2. Methods

2.1. Participants

Between July 2012 and February 2013, study participants were recruited from two inpatient wards of the Mental Health Center of the Second Xiangya Hospital in Changsha, China. Both wards are dedicated to a voluntary treatment of psychosis associated with ATS and ketamine use and they treat approximately 50 patients at any given time with a total of 600-750 admissions per year.

Study eligibility criteria included (1) men and women, aged 18 to 60 years with DSM-IV diagnosis of METH-dependence and psychosis; (2) a score ≥4 on at least one Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987) psychosis item (delusions, conceptual disorganization, hallucinatory behavior, grandiosity, or suspiciousness/persecution) and a score ≥4 (moderately ill) on the severity item of the Clinical Global Impression Scale-Severity of Illness (CGI-S) (Spitzer, Williams, & Gibbon, 1995) at the point of maximum severity of illness to date; (3) duration of psychotic symptoms for more than 2 weeks, and use of METH at least once per week during three months prior to enrollment; and (4) a positive urine screen for METH. Participants were also required to be not dependent on other substances other than nicotine and not experiencing acute intoxication effects of METH that could interfere with the informed consent process or with compliance with study procedures. Suicidal or homicidal subjects were excluded, along with those having serious medical illnesses, known hypersensitivity or allergy to aripiprazole or risperidone, documented history of having other mental illness that required treatment with antipsychotics, unstable medical conditions. Female participants of child-bearing potential had to be using a medically acceptable form of contraception, but females who were positive on a urine pregnancy test or lactating were excluded.

Of 453 patients admitted to the two wards during the study period (between July 2012 and February 2013), 125 were screened for initial eligibility, 73 were found ineligible (7 had PANSS or/and CGI-S score <4; 48 had duration of psychosis <2 week; 3 had negative urine screen for METH; 2 had other mental illness; 2 had serious medical illnesses; 4 were poly-substance users; 3 had PANSS or/and CGI-S score < 4 & duration of psychosis <2 week, 1 had PANSS or/and CGI-S score <4 and negative urine screen for METH, 1 had duration of psychosis <2 week and negative urine screen for METH; 2 had other mental illness & poly-substance use). Of the 52 eligible individuals, 42 agreed to participate and were randomized in the trial. Those who were eligible but did not participate in the trial were similar in age, race/ethnicity, and METH use to those who were randomized (data not shown).

Eligible patients who agreed to participate were randomly assigned (1:1) to either flexibly dosed aripiprazole or risperidone. The study statistician, not involved in provision of patient care created a computer-generated random allocation sequence with permuted fixed blocks of treatments. While the study participants were not informed which medication they receive, the medications were not over-encapsulated, and the doctors providing patient care at the hospital ward knew the medication group assignment for each patient. Because potential side effects often develop within the first month of medication administration, we planned to follow the patients for 25 days during their inpatient stay with frequent assessments of psychotic symptoms and potential adverse effects (on days 3, 5, 7, 10, 13, 16, 19, 22, 25 during the hospital stay).

The study was reviewed and approved by the institutional review board of the Second Xiangya Hospital, Central South University, and written informed consent was obtained from the patients or their legally authorized representatives. We planned to enroll a sample of 120 patients. However, the study was discontinued after 42 participants were enrolled due to a high rate of adverse effects and patient dropout in aripiprazole group.

2.2. Study treatments

During the first 7 days of treatment, patients assigned to treatment with aripiprazole initially received 5 or 10 mg per day, and the daily dose could be raised to up to 15 mg per day at the discretion of the attending physician, based on patient's severity of psychotic symptoms or response to the initial dose of medication. For the remaining 18 treatment days the highest dose received during the first 7 days was maintained as the treatment daily dose. All patients in the aripiprazole group reached and were maintained on 15 mg per day during their study treatment.

A similar protocol was applied for risperidone patients: they initially received between 1 and 2 mg twice a day (morning and evening), at the discretion of the attending physician and based on the patient's clinical response and tolerability risperidone could be adjusted to up to 3 mg twice a day during the first 7 days of treatment. For the remaining 18 treatment days the highest risperidone dose received during the first 7 days was maintained as the treatment daily dose. In the risperidone group, 9 participants reached 9 mg, 6 reached 5 mg, and 6 reached and were maintained on 4 mg per day.

2.3. Ancillary medications

In addition to the two study medications, 12 patients in aripiprazole and 13 in risperidone received alprazolam to treat agitation, anxiety and insomnia up to 0.8 mg per day; 8 patients in aripiprazole and 8 patients in risperidone received clonazepam, up to 2 mg per day, but not allowed in the morning prior to scheduled assessments; 11 patients in aripiprazole and 13 patients in risperidone received lithium carbonate, up to 1,000 mg per day; 11 patients in aripiprazole and 9 patients in risperidone received magnesium valproate, up to 500 mg per day (both of them were used to stabilize mood such as irritability and anxiety throughout the study); 18 patients in aripiprazole and 19 patients in risperidone received benzhexol (up to 2 mg twice a day) to attenuate the extrapyramidal symptoms induced by antipsychotics; 8 patients in aripiprazole and 9 patients in risperidone received propranolol (up to 10 mg three times a day) to improve the tachycardia (heart rate >100 per minute). One patient in aripiprazole group received an antidepressant (venlafaxine, up to 150 mg/day) and one patient in risperidone received fluoxetine (up to 20 mg/day) for treatment of depression symptoms.

2.4. Assessment instruments

Methamphetamine dependence and the METH-associated psychosis diagnoses were based on DSM-IV criteria. Psychotic symptom severity was assessed using the Positive and Negative Symptoms Scale (PANSS), and the overall severity of illness was evaluated with the Clinical Global Impression Scale Severity Subscale (CGI-S). The Visual Analogue Scale (VAS) (Grant et al., 1999) was used to assess METH craving. Severity of extra-pyramidal symptoms (EPS) were assessed by the Barnes Assessments Akathasia Rating Scale (BARS) (Barnes, 1989), and the Simpson Angus Scale (SAS) (Simpson & Angus, 1970). At each follow-up, vital signs and the body weight were also measured (not reported).