Drug and Alcohol Dependence 186 (2018) 130–137

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Atomoxetine for amphetamine-type stimulant dependence during buprenorphine treatment: A randomized controlled trial

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ARTICLE INFO

Keywords:
Amphetamine-type stimulants
Opioids
Substance use disorder
Atomoxetine
Pharmacotherapy

ABSTRACT

Background: Amphetamine type stimulants (ATS) use is highly prevalent and frequently co-occurs with opioid dependence in Malaysia and Asian countries. No medications have established efficacy for treating ATS use disorder. This study evaluated the safety, tolerability, and potential efficacy of atomoxetine for treating ATS use disorder.

Methods: Participants with opioid and ATS dependence (N = 69) were enrolled in a pilot, double-blind, placebo-controlled randomized clinical trial; all received buprenorphine/naloxone and behavioral counseling and were randomized to atomoxetine 80 mg daily (n = 33) or placebo (n = 33). The effect size of the between-group difference on the primary outcome, proportion of ATS-negative urine tests, was estimated using Cohen's d for the intention-to-treat (ITT) sample and for higher adherence subsample (≥60 days of atomoxetine or placebo ingestion).

Results: Participants were all male with mean (SD) age 39.4 (6.8) years. The proportion of ATS-negative urine tests was higher in atomoxetine- compared to placebo-treated participants: 0.77 (0.63–0.91) vs. 0.67 (0.53–0.81, d = 0.26) in the ITT sample and 0.90 (0.75–1.00) vs. 0.64 (0.51–0.78, d = 0.56) in the higher adherence subsample. The proportion of days abstinent from ATS increased from baseline in both groups ($p < 0.001$) and did not differ significantly between atomoxetine- and placebo-treated participants ($p = 0.42$). Depressive symptoms were reduced from baseline in both groups ($p < 0.02$) with a greater reduction for atomoxetine- than placebo-treated participants ($p < 0.02$). There were no serious adverse events or adverse events leading to medication discontinuation.

Conclusions: The findings support clinical tolerability and safety and suggest potential efficacy of atomoxetine for treating ATS use disorder in this population.

1. Introduction

Co-occurring amphetamine type stimulants (ATS) and opioid use is highly prevalent in Malaysia and throughout the Asian region (United Nations Office on Drugs and Crime, 2016). In Malaysia, primarily used ATS include crystalline methamphetamine and amphetamine/methamphetamine tablets (Chooi et al., 2017; Desrosiers et al., 2016). The consequences of ATS and opioid use drive major public health problems, including HIV/AIDS (Chawarski et al., 2008; Colfax et al., 2018; Degenhardt et al., 2014, 2010; Mathers et al., 2008; Mazlan et al., 2006; McKetin et al., 2008; Singh et al., 2013; Strathdee and Stockman, 2010). In Malaysia, most of the > 300,000 registered drug using individuals (estimated > 500,000 total) use heroin, morphine, or other opioids, mostly by injection, and frequently also use ATS by smoking or injection. An estimated 16.6% of people who inject drugs are infected with HIV, and injection drug use accounts for approximately 65% of HIV infections in Malaysia (105,189 registered between 1986 and 2015) (Ministry of Health Malaysia, 2010; Ministry of Health Malaysia, 2015; Ministry of Health Malaysia, 2016). In recent surveys of people who inject heroin or other opioids in Malaysia, 75% reported lifetime ATS use (21% inject ATS), and lifetime ATS use was significantly associated with HIV infection (Chawarski et al., 2012).

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https://doi.org/10.1016/j.drugalcdep.2018.01.017
Received 27 September 2017; Received in revised form 24 January 2018; Accepted 24 January 2018
Available online 10 March 2018
0376-8716/

Opioid agonist maintenance treatment with methadone or buprenorphine has been scaled up in Malaysia and other countries in the region over the past 15 years to treat opioid use disorder and reduce HIV transmission risk (Schottenfeld et al., 2008; Vicknasingam et al., 2015). Currently, approximately 380 physicians in Malaysia treat approximately 10,000 patients with buprenorphine/naloxone in general medical practice settings (Vicknasingam et al., 2015), but the effectiveness of these public health efforts may be reduced because of the high prevalence of co-occurring ATS and opioid dependence. Buprenorphine and methadone do not specifically target co-occurring ATS use, and co-occurring stimulant use is associated with more severe HIV risk behaviors, a higher prevalence of HIV infection, and high attrition from and persistent drug use during methadone or buprenorphine treatment (Corsi and Booth, 2008; Marquez et al., 2006; Molitor et al., 1999; Rawson et al., 2008; van Griensvan et al., 2004; Volkow et al., 2007). Despite the critical need, there are currently no efficacious medications for treating ATS use disorder either as a primary disorder or co-occurring with opioid use disorder (Brensilver et al., 2013; Carson and Taylor, 2014; Elkashef et al., 2008; Karila et al., 2010; Phillips et al., 2014).

Findings from pre-clinical and clinical studies support the safety, tolerability, and potential efficacy of the selective norepinephrine transporter (NET) inhibitor atomoxetine for treating ATS use disorder. Initially developed as an antidepressant medication, atomoxetine is approved to treat Attention Deficit Hyperactivity Disorder (ADHD) (Savill et al., 2015; Simpson and Plosker, 2004). Atomoxetine increases synaptic norepinephrine (NE) levels throughout the central nervous system and increases dopamine (DA) levels in the prefrontal cortex, where the NET (which binds to both NE and DA) is primarily responsible for DA reuptake (Bymaster et al., 2002; Swanson et al., 2006). Through these effects, atomoxetine targets many of the core features of ADHD that are also associated with ATS use disorder and relapse risk following discontinuation of ATS use, including impairments of executive function (attention, concentration, working memory, planning, and decision-making) and emotional dysregulation (irritability, affective lability, and emotional over-reactivity) (Economidou et al., 2009; Ersche et al., 2006; Gowin et al., 2014; Hoffman et al., 2006; Karila et al., 2010; Kohno et al., 2014; Monterosso et al., 2005; Paulus et al., 2005; Reimherr et al., 2005; Salo et al., 2007; Shoptaw et al., 2009; Sofuoglu and Sewell, 2009; Volkow et al., 2001). Human laboratory studies support the safety and potential efficacy of atomoxetine for treating ATS use disorder (Kelly et al., 2005; Lile et al., 2006; Rush et al., 2011; Sofuoglu et al., 2009), and unlike stimulant medications (amphetamine or methylphenidate) used to treat ADHD and investigated as potential treatments for ATS use disorder, atomoxetine has little to no abuse liability (Jasinski et al., 2008; Lile et al., 2006; Upadhyaya et al., 2013). One small randomized clinical trial did not find significant effects of atomoxetine compared to placebo for treating cocaine use disorder (Walsh et al., 2013), but there are no published, randomized, placebo-controlled studies of atomoxetine for treating ATS use disorder or co-occurring ATS and opioid use disorder.

Consequently, we conducted a pilot, randomized, placebo-controlled, double-blind clinical trial of atomoxetine during buprenorphine treatment of participants with co-occurring ATS and opioid dependence. The specific aims of the pilot clinical trial were to evaluate the tolerability and safety of atomoxetine and obtain estimates of its potential efficacy for reducing ATS use in this population. To conduct the pilot study and other studies of treatments for these co-occurring disorders, we first developed a substance use disorder clinical research program, including inpatient and outpatient units, at the health campus of Universiti Sains Malaysia in Kota Bharu, Malaysia. Located on the Thailand border in northeast peninsular Malaysia, Kota Bharu has experienced the most explosive growth in ATS problems over the past 5 years and has a high prevalence of ATS use (~75%) and of HIV (~45%) among people who inject opioids, and it has the highest number of women with HIV in Malaysia, suggesting that HIV is making the transition to the general population.

2. Methods

2.1. Study design

The study design was a single-site, pilot, double-blind, placebo-controlled, randomized clinical trial. Participants were treated in the inpatient program for 10 days to achieve an initial period of documented abstinence from ATS, induction and stabilization on buprenorphine/naloxone, initiation of behavioral drug counseling, and randomization (after 5–7 days) to atomoxetine or placebo. Following hospital discharge, participants were treated as outpatients for 16 weeks. The study protocol was reviewed and approved by the Human Investigation Committee of Yale School of Medicine and the Universiti Sains Malaysia Research Ethics Committee and registered as a clinical trial at https://clinicaltrials.gov/under NCT01863251.

2.1.1. Participants and location

The enrollment period lasted from March 2013 to April 2014. The study enrolled treatment-seeking volunteers meeting DSM-IV-TR criteria for both opioid and ATS dependence who reported ATS use on two or more days per week in the month prior to study admission and had opioid- and ATS-positive urine toxicology test results at study enrolment. Exclusion criteria included history of hypersensitivity to atomoxetine, narrow angle glaucoma, pheochromocytoma, or severe cardiovascular disorder, hypertension, liver enzymes greater than 3 times the upper limit of normal, liver failure or acute hepatitis, current suicide or homicide risk, current psychotic disorder or major depression or taking a neurolopetic or anti-depressant medication (including using a monoamine oxidase inhibitor (MAOI) within the preceding 2 weeks), current participation in treatment for substance use disorder, or inability to understand the protocol or assessment questions. The study population was all male because of very low prevalence of co-occurring opioid and ATS dependence among females in the region. Additionally, stigma associated with drug use among females precluded identification and enrollment of sufficient number of females in the study. One female seeking treatment was treated outside of the study protocol. All participants provided written, voluntary informed consent. All clinical and research activities were conducted at the Department of Psychiatry in the Hospital Universiti Sains Malaysia in Kota Bharu, Malaysia. Research and clinical staff were trained in the study protocol during a pre-pilot phase and treated 13 participants with buprenorphine/naloxone and open-label atomoxetine in the pre-pilot phase before the start of the pilot randomized clinical trial.

2.1.2. Randomization and masking

The simple randomization sequence was computer-generated in the US by an investigator who had no contact with study participants (MCC). To allow sufficient time for preparation of study medications (active and placebo), treatment group assignment was communicated to the study pharmacist at Hospital Universiti Sains Malaysia, who also had no direct contact with participants or clinical staff, approximately 2 days in advance of administering the first dose of atomoxetine or placebo. Atomoxetine 40 mg tablets were purchased from the local distributor. The study pharmacist prepared identical-appearing capsules containing atomoxetine 40 mg or placebo. Atomoxetine was crushed and packed into empty capsules, and sodium bicarbonate was used for placebo.

2.1.3. Interventions

2.1.3.1. Buprenorphine/Naloxone (8 or 2 mg, containing buprenorphine and naloxone in 4:1 ratio) induction and maintenance (all participants). Participants were inducted onto buprenorphine/naloxone with an initial dose of 4 mg administered when the participant was exhibiting mild signs of withdrawal during day one of