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The efficacy of atomoxetine as adjunctive treatment for co-morbid substance use disorders and externalizing symptoms☆

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ABSTRACT

Background: We examined the effect of atomoxetine supplementation in treated-as-usual patients with alcohol, tobacco and other drug dependence (ATOD) and co-morbid externalizing symptoms (ES).
Method: Subjects were selected from a substance dependence treatment-cohort and assessed for: (a) high ES counts, (b) maximum prior period of abstinence, (c) quality of life during that period, and (d) shortest time from prior relapse to restarting treatment. Subjects were prescribed atomoxetine and followed up to their first relapse.
Results: Out of 262 subjects screened during the study period (March–April 2008), 18 subjects who fulfilled eligibility criteria were recruited. All subjects were male, with early onset of substance dependence to at least two substances. Atomoxetine treatment led to significant treatment benefits: ES reduction, longer abstinence, shorter turnaround time and better quality of life.
Conclusions: Atomoxetine has a potential role in the treatment of early onset ATOD patients with ES, as an adjuvant to the standard treatment.

1. Narrative

1.1. Background

Alcohol, tobacco and other drug dependence (ATOD), childhood conduct disorders (CD), attention-deficit hyperactivity disorders (ADHD), and adult antisocial behavior commonly occur in combination (Carroll and Rounsaville, 1993; Biederman et al., 1998; Schubiner et al., 2000; Sullivan and Rudnik-Levin, 2001; Barkley et al., 2004; Knop et al., 2009). Various estimates have reported between 20% and 50% co-morbidity in ATOD and ADHD (Johann et al., 2003; Ohlmeier et al., 2008). Studies suggest that comorbid ATOD and ADHD forms a distinct clinical phenotype characterized by an increased severity of substance-related symptoms and behavioral/emotional problems, longer course, and greater difficulty in achieving abstinence and to remain in treatment. ADHD is also associated with a higher risk of early development of alcohol and other drug dependence (Wilens et al., 1997; Johnson et al., 2000; Johann et al., 2003; Ohlmeier et al., 2008).

Available evidence, from twin/family studies, electrophysiological and neuro-imaging studies, suggest that a shared genetic neurobiological diathesis, which manifests as a behavioral-temperamental trait, characterized by ADHD symptoms (inattention, impulsivity), oppositional behavior and/or conduct problems, constitutes a vulnerability for ATOD, and has been called the externalizing psychopathology (Silva et al., 2007; Dick et al., 2008). Intuitively, this evidence should make a strong case for concurrent treatment of at least the ADHD symptoms in persons with comorbid ATOD and externalizing psychopathology. Yet, there is a paucity of literature on such concurrent treatment strategies (Wilson and Levin, 2005). A meta-analysis of pharmacotherapy in ADHD youth found a 1.9-fold reduction in risk for ATOD in those treated with stimulants, compared with youth who did not receive pharmacotherapy (Wilens et al., 2003), while another randomized control trial of stimulant treatment in persons with ATOD and co-morbid ADHD showed no significant difference between medication and control groups (Schubiner et al., 2002).

Atomoxetine is a noradrenergic agent approved for the treatment of children and adults with ADHD (Michelson et al.,

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2001, 2003). A selective inhibitor of presynaptic norepinephrine transporter in the central nervous system, it was found to be more efficacious than placebo in reducing ADHD symptoms, equally efficacious in head-to-head trials with stimulants and had low discontinuation rates even in doses up to 120 mg (Spencer et al., 1998; Michelson et al., 2003). Atomoxetine, unlike stimulants, is free of abuse potential (Heil et al., 2002) and therefore, of special interest in comorbid ATOD (Wilens, 2004). Adverse effects include appetite suppression, initial weight loss, initial tachycardia and increase in blood pressure which stabilizes later, drowsiness, dizziness, light headedness and fainting (Unni, 2006; Adler, 2007). A 3-month double blind placebo controlled study of adult alcohol use disorder with comorbid ADHD found that atomoxetine significantly reduced ADHD symptoms compared to placebo, but with no significant differences between treatment groups in time-to-relapse of heavy drinking. However, cumulative heavy drinking days were reduced by 26% in the atomoxetine group (Wilens et al., 2008). In addition, ADHD score reductions were found to correlate with decrease in alcohol craving; this was more notable with atomoxetine than placebo (Wilens et al., 2011). Open-label studies found treatment with atomoxetine to be of limited utility in the treatment of cannabis and cocaine dependence (Tirado et al., 2008; Levin et al., 2009).

We sought to examine the effect of atomoxetine supplementation in subjects with co-morbid ATOD and externalizing symptoms (ES), belonging to a long-term treatment cohort, currently in treatment (with pharmacological and behavioral interventions). We used a dimensional score for ES using the World Health Organization Adult ADHD Self-Report Scale (ASRS) (Kessler et al., 2005) rather than using a categorical diagnosis of ADHD.

2. Methodology

2.1. Sample

The study used a within-subject retrospective design with naturalistic follow-up. Subjects were recruited from the outpatient services of the Deaddiction Center, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India, during the months of March and April 2008. During this period, all consecutive, who presented with a relapse during this time-window were screened, and included in the study if they: (1) satisfied dependence criteria for at least one substance (other than nicotine) according to the International Classification of Diseases, version 10 [ICD-10] (WHO, 1992), (2) had available records of past treatment and outcome in the database, (3) had score of 24 or more on the World Health Organization Adult ADHD Self-Report Scale–version 1.1 (ASRS) (Kessler et al., 2005), (4) were never treated for ADHD, (5) were above 18 years and, (6) did not have a history of comorbid psychosis, mood or anxiety disorders and seizures. The study was conducted in accordance with the Declaration of Helsinki and subjects were recruited after written informed consent.

2.2. Methodology

Subjects were assessed using the following measures

(A) ASRS for the measurement of ES.
(B) A life chart for each patient constructed from the treatment records and corroborated with the subjects and significant family members. The previous period of maximum abstinence (from any substance other than nicotine) on the ongoing treatment regime was identified and quantified. Nicotine was universally used by all study subjects, and abstinence had never been achieved with past or current treatment. Also the minimum turnaround time (defined as the minimum time required to re-engaging in treatment after any relapse on any previous treatment in the past 2 years) was quantified.
(C) The World Health Organization Quality of Life—WHOQOLBREF scale (WHO, 1998) was used with individual subjects to derive retrospective information about quality of life during the abstinence period.
(D) Subjects were also asked to make a subjective evaluation of effectiveness of treatment on a visual analog scale of 0–10 from not effective at all to extremely effective.
(E) Side effects checklist—constructed from known symptoms and signs of adverse effects of atomoxetine available in the literature (Appendix A) was applied for subsequent monitoring during out-patient visits.

Assessments were done during a brief (3 weeks) inpatient admission after the subject was re-engaged in the treatment process. After completion of the inpatient detoxification for control of withdrawal symptoms (usually completed in 7–10 days), ratings on measures A–D were performed. This was followed by addition of atomoxetine to the treatment regime which was in use prior to the current relapse (combination of long-term pharmacotherapy and relapse prevention therapy). All subjects were required to come thereafter for out-patient monitoring visits, to facilitate incremental changes in the dosage of atomoxetine, up to a maximum of 50 mg/day, and assessment of emergent adverse effects, rated on the side effects checklist. Subjects continued to receive 'treatment as usual' (TAU), which consisted of pharmacological treatments prescribed previously as well as relapse prevention counseling.

All measures were reapplied after the baseline measurements during the outpatient visit in the sixth week. The subjects were then followed up every 2 months till their next relapse and re-engagement into treatment, or for a period of 1 year, whichever occurred earlier. Relapse was ascertained by interviewing the patient and at least one family member living with the patient. In case of doubt, urine testing was carried out to detect the substance.

2.3. Statistical analysis

The paired '*t*'-test was used to compare (1) the period of abstinence with atomoxetine with past maximum period of abstinence (on TAU without atomoxetine), (2) the shortest previous turnaround time with current turnaround time where applicable, (3) the ES scores at baseline and 6 weeks, (4) the WHOQOL BREF scores during past abstinence with scores during current abstinence and (5) well as the subjective ratings on treatment efficacy. A p value of <0.05 was considered statistically significant.

3. Results

3.1. Sample characteristics (Table 1)

Of 262 subjects screened during the study period, 18 fulfilled eligibility criteria and were recruited after obtaining written informed consent. All subjects were male, with early onset (<25 years) of substance dependence and were dependent on at least two substances. In addition to having high ES scores, clinical interview by an experienced psychiatrist (VB) showed that majority (13/18, 72%) of them also had a DSM-IV diagnosis of ADHD. Clinical interviews also revealed that the ES were of childhood onset in all patients.

The mean dose of atomoxetine was 41.9 ± 13.7 mg/day. Four of the subjects did not return after initial assessment during inpatient care (no follow-ups) and hence, were excluded from the analysis of