A review of the abuse potential assessment of atomoxetine: a nonstimulant medication for attention-deficit/hyperactivity disorder

Himanshu P. Upadhyaya · Durisala Desaiah · Kory J. Schuh · Frank P. Bymaster · Mary J. Kallman · David O. Clarke · Todd M. Durell · Paula T. Trzepacz · David O. Calligaro · Eric S. Nisenbaum · Paul J. Emmerson · Leslie M. Schuh · Warren K. Bickel · Albert J. Allen

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Abstract

Rationale  Treatment of attention-deficit/hyperactivity disorder (ADHD) has for many years relied on psychostimulants, particularly various formulations of amphetamines and methylphenidate. These are central nervous system stimulants and are scheduled because of their abuse potential. Atomoxetine (atomoxetine hydrochloride; Strattera®) was approved in 2002 for treatment of ADHD, and was the first nonstimulant medication approved for this disorder. It was classified as an unscheduled medication indicating a low potential for abuse. However, the abuse potential of atomoxetine has not been reviewed.

Objectives  In this article, we review the evidence regarding abuse potential of atomoxetine, a selective inhibitor of the presynaptic norepinephrine transporter, which is unscheduled/unrestricted in all countries where it is approved.

Methods  Results from receptor binding, in vitro electrophysiology, in vivo microdialysis, preclinical behavioral, and human laboratory studies have been reviewed.

Results  Atomoxetine has no appreciable affinity for, or action at, central receptors through which drugs of abuse typically act, i.e., dopamine transporters, GABA_A receptors, and opioid μ receptors. In behavioral experiments in rodents, atomoxetine does not increase locomotor activity, and in drug discrimination studies, its profile is similar to that of drugs without abuse potential. Atomoxetine does not serve as a reinforcer in monkey self-administration studies, and human laboratory studies suggest that atomoxetine does not induce subjective effects indicative of abuse.

Conclusion  Neurochemical, preclinical, and early clinical studies predicted and supported a lack of abuse potential of atomoxetine, which is consistent with the clinical trial and postmarketing spontaneous event data in the past 10 years.

Keywords  Atomoxetine (Strattera®) · ADHD · Abuse potential · Nonstimulant

Introduction

Attention-deficit/hyperactivity disorder (ADHD) (APA 2000) is an early onset childhood disorder that is estimated to occur in 3 % to 9 % of children and adolescents in the
USA (Faraone et al. 2003; Greydanus et al. 2007) and 4 % to 8 % worldwide (Kessler et al. 2006; Smoot et al. 2007).

Frequently associated with impaired academic and social functioning, ADHD persists into adulthood in 50 % to 70 % of affected youth (Barkley et al. 2002; Hechtman 2000). For decades, management of ADHD relied primarily on psychostimulants, such as amphetamines and methylphenidate, for which short- and long-acting formulations are available through a wide variety of branded and generic manufacturers. Although their efficacy is well documented, psychostimulants are controlled substances because of their documented abuse potentials. Amphetamines and methylphenidate are currently classified as schedule II drugs by the US Controlled Substance Act (CSA), indicating that while they have an approved medical use, they also have significant abuse liabilities, which raises concerns about nonmedical use in patients with ADHD, including misuse, abuse, or diversion to individuals without ADHD (Substance Abuse and Mental Health Services Administration 2006; The National Center on Addiction and Substance Abuse at Columbia University 2007). A wide range of drug classes subject to regulation under the CSA including central nervous system depressants and stimulants. CSA requires an eight-factor analysis for all scheduling decisions by the Drug Enforcement Administration (http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM180870.pdf). This analysis includes factors such as its actual or relative potential for abuse; pharmacological effect; other current scientific knowledge; history and current pattern of abuse; scope, duration, and significance of abuse; public health risk; psychic or physiological dependence potential; and if the drug is an immediate precursor of a controlled substance under section 21 USC 811(c). Scheduling of a drug regulated under CSA can influence prescribing, utilization, and manufacturing requirements of that drug.

Atomoxetine is a selective inhibitor of the presynaptic norepinephrine (NE) transporter, with minimal affinity for noradrenergic receptors or other neurotransmitter transporters or receptors (Bymaster et al. 2002). In 2002, it was approved by the US Food and Drug Administration (FDA) as an uncontrolled, nonstimulant treatment for pediatric, adolescent, and adult ADHD (Michelson et al. 2002, 2003; Spencer et al. 1998, 2002). Atomoxetine has been shown to be efficacious for the treatment of ADHD with a favorable safety profile (Simpson and Plosker 2004; Garnock-Jones and Keating 2010).

Recently, extended release formulations of two nonstimulant α(2A)-adrenoceptor agonists guanfacine and clonidine, have been approved in the USA for the treatment of ADHD in children and adolescents. Like atomoxetine, both guanfacine and clonidine have not been scheduled as controlled substances (http://pi.shirecontent.com/PI/PDFS/Intuniv_USA_ENG.pdf; http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/017407s034lbl.pdf).

In addition to concerns regarding diversion of prescribed medications, treatment of patients with ADHD, especially adolescents and adults, is complicated by their high comorbidity for substance use disorders (Biederman et al. 1997; Molina and Pelham 2003; Shekim et al. 1990; Upadhyaya et al. 2005; Wilens et al. 1997). Its effect on neurobiological pathways suggests that atomoxetine has less abuse potential than stimulants (Wee and Woolverton 2004) due to its lack of increase of dopamine (DA) transmission in the mesolimbic and mesocortical pathways up to the nucleus accumbens (NAc) (Bymaster et al. 2002; Simpson and Plosker 2004). Previous reviews have demonstrated that atomoxetine is useful for patients at risk of substance abuse or who do not wish to take a controlled substance: atomoxetine is effective, has a favorable safety profile, and has a negligible risk of abuse or misuse (Garnock-Jones and Keating 2010; Simpson and Plosker 2004). However, a comprehensive review of abuse potential assessments of atomoxetine compared with psychostimulant drugs has not been published. In this review article, we review previously published literature on abuse potential testing for atomoxetine and present research findings that demonstrate the low abuse potential of atomoxetine in contrast to psychostimulant medications, such as amphetamine and methylphenidate.

Neurobiology of stimulant action

The mesolimbic and mesocortical pathways, both part of the brain reward circuitry, connect the structures that are thought to control and regulate stimulant activity and behavior. The mesolimbic system extends from the ventral tegmental area via the medial forebrain bundle to the NAc, which is the primary release site for DA (Koob 1992).

Amphetamines and methylphenidate have similar effects on DA and NE neurotransmission (Kahlig et al. 2005; Simpson and Plosker 2004). Both substances primarily increase DA and, to a lesser degree, noradrenergic activity in neural systems. Both block presynaptic reuptake of DA, resulting in higher synaptic levels, as suggested by microdialysis studies (Bredeloux et al. 2007; Bymaster et al. 2002; Koda et al. 2010; Mazei et al. 2002; Pontieri et al. 1995). Amphetamine also causes nonvesicular release of DA through the dopamine transporter (DAT) by promoting the exchange for cytosolic DA (Partilla et al. 2006; Sandoval et al. 2002). Amphetamine causes DAT-mediated DA efflux by two independent mechanisms: (1) a slow process consistent with an exchange mechanism and (2) a process that results in rapid (milliseconds) bursts of DA efflux that is comparable to transport through a channel such as DAT. This rapid release of large numbers of DA molecules plays a role in the synaptic actions and psychostimulant effects of amphetamine and related compounds (Kahlig et al. 2005).
Therapeutic doses of oral methylphenidate can effectively block DATs (Volkow et al. 1998) and significantly increase extracellular DA (Volkow et al. 2001) in humans. An evaluation of the levels of DAT blockade is important in light of the evidence that DATs are involved in mediating the reinforcing effects of cocaine (Ritz et al. 1987). Volkow et al. (1997) demonstrated that the extent and time course of DAT occupancy in human volunteers who abuse cocaine correlated with the “high” subjective effect of cocaine. A review of its clinical use and abuse indicated that reinforcing effects of methylphenidate may be attributed to large and rapid increases in extracellular DA, whereas therapeutic effects occur when the drug elicits slow, steady-state DA increase (Volkow and Swanson 2003).

Evidence for abuse potential of stimulants

Prevalence rates Comprehensive reviews on this subject are provided in the publications by Kollins (2007) and Wilens et al. (2008a). In 2005, the Drug Abuse Warning Network (Substance Abuse and Mental Health Services Administration 2007) estimated that stimulants, including amphetamines, were involved in 138,950 emergency department visits; the rates were highest among patients 18 to 44 years old. Further, the annual prevalence rate for amphetamine use among US 12th graders was reported to be 8.2 % in 2011 (Johnston et al. 2012). The trend of amphetamine use among college students has increased from 4.2 % in 1996 to 9.0 % in 2010 (Johnston et al. 2009, 2011). Further, the annual prevalence rates for methylphenidate use in 8th, 10th, and 12th graders was reported to be 1.6 %, 2.9 %, and 3.4 %, respectively (Johnston et al. 2008). While among college-aged students, the prevalence of illicit methylphenidate use was 4.2 % in 2005 (Johnston et al. 2009).

A study based on Internet-based epidemiological survey evaluated the prevalence of nonmedical use of prescription medications for ADHD (Novak et al. 2007). This study reported that ~7.01 % of US adults aged 18–49 years used a stimulant ADHD medication for nonmedical purpose at least once in their lifetime. The prevalence of nonmedical use was more for short-acting stimulants versus long-acting ones. Although the original study reported productivity as the most frequent reason for nonmedical use of ADHD medication (Novak et al. 2007), a post hoc analysis revealed that a substantial proportion of young adults may be using stimulants for self-medication of ADHD symptoms (Upadhyaya et al. 2010). The motivation for nonmedical use of immediate- and extended-release formulations of stimulants may be distinct, such as recreational versus productivity. Irrespective of the intended nonmedical use, friends and family remain an important source for diverted medication (Novak et al. 2007; Upadhyaya et al. 2010).

Adverse effects Adverse events related to various forms of amphetamines include abuse, dependence, and neurotoxicity. Evidence indicates that the adverse effects observed in humans and experimental animals can be explained by the critical role of amphetamines on DA and NE. These include arousal, hyperactivity, stereotypic perseverative movements, psychomotor depression, cognitive impairment, hallucinatory-like behaviors, and chronic self-administration (Berman et al. 2009). Chronic administration has also shown neurotoxicity that can persist for years, such as deficits in phenotypic markers for dopaminergic nerve terminals, enlarged chromatolytic medulla neurons in cats, and swollen or reduced dopaminergic axons, and serotonin deficits in rodents (Berman et al. 2009).

Self-administration, reinforcing, and subjective effects Human abuse potential has been well predicted through the animal self-administration model paradigms. Methylphenidate was self-administered by nonhuman primates (Bergman et al. 1989; Johanson and Schuster 1975; Wilson et al. 1971) and humans (Jasinski et al. 2008). In a human laboratory study (Jasinski et al. 2008), methylphenidate produced significant positive effects and drug-liking. Both intranasal (Garland 1998; Massello and Carpenter 1999) and intravenous (Parran and Jasinski 1991) use of methylphenidate have also been reported. This is further confirmed by the results of a placebo-controlled human laboratory study that examined the reinforcing and subjective effects of methylphenidate and D-amphetamine in non-drug-abusing subjects (Rush et al. 2001). It was demonstrated that methylphenidate and D-amphetamine could function as reinforcers and produce stimulant-like subjective effects, leading to abuse potential. Both drugs produced comparable subject-rated drug effects, including increased A scores on the Addiction Research Center Inventory (ARCI), increased ratings of “any effect” and “like drug” on the subject-rated drug-effect questionnaire. Although, in this study the reinforcing and subject-rated drug effects with methylphenidate were observed only at the highest dose tested (40 mg), this did not undermine its drug abuse potential. Thus, the existing evidence, including surveys and controlled laboratory conditions, indicates that amphetamines and methylphenidate have significant abuse potential.

Atomoxetine: lack of evidence for abuse potential

Various biochemical, pharmacological (e.g., receptor binding, in vivo microdialysis), and behavioral studies in animals, and human studies that measured the subjective effects of atomoxetine have been conducted to assess its potential for abuse potential. Stimulant-induced increases in extracellular DA levels, especially in the NAc, plays an
important role in their drug abuse potential, and therefore, atomoxetine was examined for its effect on extracellular levels in the NAc as well as various neuronal receptor activities. The methods and results of these studies are described in the following sections.

**Receptor binding studies**

Receptor-binding studies may be used to determine the binding affinity of an active substance to known targets involved in drug dependence (e.g., opioid receptors, 5-HT, and dopamine transporters and receptors, NMDA, GABA, nicotinic acetylcholine, and cannabinoid receptors). The agonist or antagonist effects of binding to a receptor can be determined by functional assays at the cellular level. Studies assessing the affinity and functional effects of atomoxetine on target receptors are presented below.

The inhibition constant \( K_i \) values, lower values indicate greater affinity) of atomoxetine for binding of ligands to monoamine uptake transporters (Bymaster et al. 2002) was \( K_i = 5.4 \text{nM} \) for the human NE transporter, \( K_i = 87 \text{nM} \) for human serotonin (5-HT; see section “In vivo animal studies”), and \( K_i = 1451 \text{nM} \) for DATs. Atomoxetine also has a low affinity for a number of other binding sites, suggesting selectivity for the NE transporter. In contrast, methylphenidate has higher affinity for the human DA transporter (\( K_i = 34 \text{nM} \)) than for the NE transporter (\( K_i = 339 \text{nM} \)). The binding affinities of atomoxetine and other agents for the DA and NE transporter, compiled from several publications, are provided in Table 1. The ratio of \( K_i \) values for DA and NE transporters reveals that several nonscheduled drugs, including atomoxetine, have much higher ratio values compared with scheduled stimulants (methylphenidate, D-amphetamine, and cocaine), whose ratios are less than 1.0. In contrast, the ratio for atomoxetine is 342, indicating much higher affinity for the NE than DA transporter and therefore suggesting a lower potential for DA-mediated substance abuse.

In addition, the binding affinity and functional activity of atomoxetine and its major metabolite, 4-hydroxyatomoxetine, was assessed at 63 neuronal receptors and binding sites, including neurotransmitter receptor sites such as the opioid \( \mu \) receptor, second messengers, ion channels, transporters, and brain and gut peptides (Bymaster et al. 2002). Atomoxetine at 1 \( \mu \text{M} \) did not inhibit any of these receptors by more than 50 \%, except binding to opioid \( \sigma_1 \) receptor, which was inhibited by 51.4 \%. The 4-hydroxyatomoxetine metabolite (1 \( \mu \text{M} \)) inhibited radioligand binding to opioid \( \delta_1 \), \( \kappa_1 \), and \( \mu \) receptors by 52 \%, 59 \%, and 66 \%, respectively. In a separate experiment, 4-hydroxyatomoxetine was found to have relatively low affinity for these same three receptors, with \( K_i \) values of 300 nM, 95 nM, and 422 nM, respectively (Bymaster et al. 2002).

**Electrophysiological studies**

Drugs with abuse potential include sedative/hypnotic drugs, whose mechanism of action are thought to involve the agonistic action on \( \gamma \)-aminobutyric acid (GABA\(_A\)) receptors (Bergman et al. 2000). Although atomoxetine had low affinity for GABA\(_A\) and benzodiazepine receptors in binding studies (Bymaster et al. 2002), the potential actions of atomoxetine on GABA\(_A\) receptors were further evaluated using electrophysiological recording of GABA\(_A\) receptor-dependent activity of ventrobasal thalamic relay neurons in a rat brain slice preparation (Zhang et al. 1997).

The possibility that atomoxetine (10 \( \mu \text{M} \)) might act as an agonist, antagonist, or allosteric modulator of GABA\(_A\) receptors was assessed by recording changes in either the resting membrane potential of ventrobasal neurons associated with GABA\(_A\) receptor activity or the inhibitory postsynaptic potentials (IPSPs) evoked by electrical stimulation of the GABA-ergic inputs from the ventrobasal neurons of the reticular thalamic nucleus (Zhang et al. 1997). Possible direct agonist actions of atomoxetine (1 and 10 \( \mu \text{M} \)) were evaluated by measuring changes in the resting membrane potential of neurons before and during compound application. In these experiments, selected concentrations of the GABA\(_A\) receptor agonist muscimol (1 \( \mu \text{M} \)), the GABA\(_A\) receptor antagonist bicuculline methochloride (10 \( \mu \text{M} \)), and the GABA\(_A\) receptor allosteric modulator pentobarbital (10 \( \mu \text{M} \)) were used as positive controls for agonist, antagonist, and potentitizer activity, respectively (Zhang et al. 1997).

Identical experiments were performed using nisoxetine hydrochloride (1 \( \mu \text{M} \) and 10 \( \mu \text{M} \)), another selective NE transporter inhibitor, which is widely used in scientific research as a standard selective NE reuptake inhibitor (Graham and Langer 1992). Results showed that atomoxetine (concentrations up to 10 \( \mu \text{M} \)) did not alter the IPSPs in ventrobasal neurons evoked by electrical stimulation of the slice preparation (Fig. 1a). However, in the same neurons, pentobarbital (10 \( \mu \text{M} \)) enhanced and bicuculline methochloride (10 \( \mu \text{M} \)) blocked GABA\(_A\) receptor-dependent IPSPs. Atomoxetine (1 \( \mu \text{M} \)) also did not affect the membrane potential of ventrobasal neurons, whereas muscimol (1 \( \mu \text{M} \)) hyperpolarized and bicuculline methochloride (10 \( \mu \text{M} \)) blocked the hyperpolarization in these same neurons (Fig. 1b). In addition, nisoxetine (1 \( \mu \text{M} \) and 10 \( \mu \text{M} \)) did not affect the membrane potential or IPSPs evoked in ventrobasal neurons (data not shown). Collectively, these data are consistent with in vitro binding studies and indicate that atomoxetine does not have agonist, antagonist, or positive allosteric actions at GABA\(_A\) receptors.

**In vivo animal studies**

**Rat neurotransmitter studies** Bymaster et al. (2002) examined atomoxetine’s ability to block neurotransmitter...
depletion in a rat brain induced by monoamine transporter-dependent neurotoxins. After rats were injected with the 5-HT selective neurotoxin p-chloramphetamine hydrochloride (p-CA), whole brain 5-HT concentrations were measured using high-pressure liquid chromatography with electrochemical detection (HPLC-EC). Results showed that atomoxetine did not block depletion of rat brain 5-HT produced by p-CA, indicating that atomoxetine does not significantly block 5-HT transporters in vivo. To measure the ability of atomoxetine to block NE uptake, the NE transporter-requiring neurotoxin N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine hydrochloride (DSP-4) was injected. Cortical NE concentrations were measured 6 h after injection and analyzed using HPLC-EC. Atomoxetine dose-dependently and potently blocked depletion of NE in the rat hypothalamus by DSP-4, demonstrating blockade of NE transporters in vivo.

In vivo microdialysis is an important technique, which helps in the elucidation of the neurochemical profile, mechanism of action, and effects of several drugs on neurotransmitter systems. This technique is used to measure drug-induced changes in concentrations of neurotransmitters such as acetylcholine, glutamate, GABA, and monoamines, and their respective metabolites in the extracellular fluid in discrete brain regions (Darvesh et al. 2011). In vivo microdialysis studies in conscious rats (Bymaster et al. 2002) showed that extracellular concentrations of NE in the

**Table 1** Binding affinity of atomoxetine, other norepinephrine transporter inhibitors, and psychostimulants for the norepinephrine and dopamine transporters compiled from several publications

| Compound        | $K_i$ (nM), mean | Ratio DAT/NET |
|-----------------|-----------------|--------------|
| **Unscheduled** |                 |              |
| Atomoxetine     | 3.7 (5.4, 2.0)  | 1,266 (1,451, 1,080) |
| Desipramine     | 2.4 (3.8, 3.5, 1.6, 0.8) | >2,295 (>10,000, 1,400, 3,190) |
| **Scheduled**   |                 |              |
| Methylphenidate | 427 (339, 514)  | 46 (34, 84, 21) |
| d-Amphetamine   | 257              | 190          |
| Cocaine         | 2,100            | 180 (120, 240) |

Abbreviations: DAT = dopamine transporter; NET = norepinephrine transporter

*a* Bymaster et al. (2002)

*b* Tatsumi et al. (1997)

*c* Gatley et al. (1996)

*d* Cheetham et al. (1996)

*e* Pristupa et al. (1994)

**Fig. 1** Atomoxetine does not affect a GABA-ergic IPSPs or b the resting membrane potential of ventrobasal thalamic neurons in rat brain slices. Data points reflect percentage of control in a and mean ± SD in b.

* Significant difference from control at p ≤ 0.05.

Abbreviations: AUC = area under the curve; GABA = γ-aminobutyric acid (GABA); IPSP = inhibitory postsynaptic potential (IPSP); SD = standard deviation

<fig1>  ![Graph](https://example.com/fig1.png)
</fig1>

<tab1>  | Atomoxetine | Muscimol |
|--------|------------|----------|
| 1 μM   | ![Graph](https://example.com/fig1.png) | ![Graph](https://example.com/fig2.png) |
| 10 μM  | ![Graph](https://example.com/fig1.png) | ![Graph](https://example.com/fig2.png) |
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prefrontal cortex were increased in a dose-dependent fashion by atomoxetine, whereas the extracellular concentrations of 5-HT were not significantly altered by atomoxetine up to 3 mg/kg (intraperitoneal administration) in the brain regions examined including the prefrontal cortex, NAc, and striatum. Furthermore, atomoxetine increased extracellular concentrations of DA to about the same magnitude as NE in the prefrontal cortex; this was attributed to the finding that DA in the prefrontal cortex is taken up by NE transporters (Di Chiara et al. 1992). Higher doses of atomoxetine produced greater and long-lasting increases in extracellular NE and DA in the prefrontal cortex than lower doses.

However, atomoxetine did not increase extracellular DA in the DA-rich NAc or striatum (Bymaster et al. 2002). In contrast to atomoxetine, methylphenidate increased extracellular DA in the NAc, an activity implicated in the reward and reinforcing aspects of this drug (Table 2) (Kuczenski and Segal 1997, 1999). Similar results with atomoxetine microdialysis studies were found in mice (Koda et al. 2010). The importance of microdialysis studies is underscored in a recent review of nonhuman primate imaging studies that found considerable evidence supporting that drug-induced reinforcing effects, DAT occupancy, and increases of extracellular DA levels were closely related (Mumane and Howell 2011).

The immediate-early gene c-fos and its protein products have been increasingly utilized as markers for neuronal activation (Dragunow and Faull 1989; Morgan and Curran 1990; Robertson et al. 1994). Hence, the expression of the neuronal activity marker Fos after atomoxetine administration was determined in several brain regions (Bymaster et al. 2002). In the atomoxetine studies, immunohistochemical localization of the Fos protein allowed the quantification of activated cells in specific forebrain nuclei following vehicle or atomoxetine administration. Atomoxetine significantly and robustly increased the number of Fos-positive cells in the prefrontal cortex (80±28 vehicle versus 296±26 atomoxetine, p ≤ 0.001), but not in the NAc and striatum (Bymaster et al. 2002). In contrast, methylphenidate induced Fos expression in the striatum of cats (Lin et al. 1996) and persistent c-fos in the NAc and in the frontal cortex of the immature rat brain (Chase et al. 2005). In another study, methylphenidate increased c-fos expression predominately in the sensorimotor striatum, but not in the NAc (Yano and Steiner 2005).

Thus, both the pattern of increase of DA in only the prefrontal cortex as well as increased Fos expression in the prefrontal cortex, but not in the NAc and striatum, indicates a unique profile for atomoxetine compared with methylphenidate that may be related to atomoxetine’s low abuse potential.

**Drug discrimination paradigm** In drug discrimination models, animals are trained to discriminate effects of a particular drug of abuse. Such models have also been used to indicate how prominent the role of DA reuptake blockade is for the abuse potential of a particular drug (Kleven et al. 1990; Rowlett et al. 2007). A number of drug discrimination studies have been conducted in rats (Terry et al. 1994).

| Table 2 Summary of abuse potential parameters for atomoxetine compared with stimulants, methylphenidate and amphetamine |
|---------------------------------------------------------------|
| **Animal studies**                                            |
| In vivo microdialysis studies                                 |
| Did not increase extracellular DA in the DA-rich NAc or striatum<sup>a</sup> | Increased extracellular DA in the NAc<sup>a</sup> | Increased extracellular DA in specific regions of the brain<sup>b</sup> |
| Self administrative behaviour<sup>a</sup>                    |
| No self administration observed                               | Doses greater than 0.03 mg/Kg produced self-administration | Doses greater than 0.03 mg/Kg produced self-administration |
| Human studies                                                |
| Subjective-drug effects<sup>d</sup>                          |
| 90-mg dose increased “bad” and “sick” portions of VAS, and LSD subscale on ARCI; not observed with lower doses (20 mg and 45 mg) | 40-mg dose increased stimulant portions of VAS and ARS, and | – |
| Discriminative stimulus<sup>e</sup>                          |
| Partially substituted for methylphenidate (33 %–50 %); stimulant-like drug effects were lower compared to stimulants (methylphenidate and D-amphetamine) | Increased drug-appropriate responding and produced stimulant-like effects | Increased drug-appropriate responding and produced stimulant-like effects |

**Abbreviations:** ARCI = Addiction Research Center Inventory; ARS = Adjective Rating Scale; DA = dopamine; LSD = lysergic acid diethylamine; NAc = nucleus acumbens; VAS = Visual Analog Scale

<sup>a</sup> Bymaster et al. (2002)
<sup>b</sup> Jones et al. (2000)
<sup>c</sup> Gasior et al. (2005)
<sup>d</sup> Heil et al. (2002)
<sup>e</sup> Lile et al. (2006)
pigeons (Johanson and Barrett 1993; Sasaki et al. 1995; Zhang and Barrett 1991), and monkeys (Kleven et al. 1990; Spealman 1995; Tidey and Bergman 1998) to evaluate the subjective effects produced by atomoxetine and the results overall suggest that atomoxetine has a low abuse potential. Two discrimination studies in pigeons (Johanson and Barrett 1993; Sasaki et al. 1995) reported the generalization of atomoxetine with cocaine (1.0 or 1.7 mg/kg) or methamphetamine (1.0 or 1.7 mg/kg). In both of these studies, atomoxetine generalized at some dose but generalization was not dose-responsive and was always accompanied by reductions in response rate or a disruption of performance. Cocaine itself produces full generalization and yet is devoid of effects on response rate at the same doses (Terry et al. 1994). Johanson and Barrett (1993) concluded that dopaminergic as well as noradrenergic systems in the pigeons mediate the discriminative stimulus effects of cocaine, while serotonergic systems do not seem to be involved in this response. It was also concluded that NE and DA reuptake inhibition and 5-HT release mediate the discriminative stimulus effects of methamphetamine (Johanson and Barrett 1993; Sasaki et al. 1995). However, data from pigeons is of questionable value in extrapolating to humans, as the pharmacology in this avian species has been shown to differ from that of rodents and primates. In rats and monkeys, when a very low dose of cocaine is used as a training stimulus, atomoxetine has been seen to occasionally generalize to cocaine (Spealman 1995; Terry et al. 1994), but as the training dose of cocaine was escalated to levels that produce frank psychomotor stimulation, the generalization was lost. Furthermore, the generalization sometimes observed with atomoxetine contrasts with that of abused stimulants. While cocaine produced 100 % effects in the rat drug discrimination model, atomoxetine did not generalize to this extent (Terry et al. 1994). Atomoxetine and nisoxetine (another NE reuptake inhibitor) substituted for cocaine in these rats, suggesting NE involvement in the discriminative stimulus effects of low doses of cocaine. Moreover, the generalization was produced only at doses of atomoxetine that had effects on other aspects of behavior (response rates) that question the validity of data interpretation. It is noteworthy that the doses of atomoxetine and nisoxetine that generalized to cocaine also produced substantial decreases in the response rate to about 20 % of the control. However, other drug discrimination studies using cocaine at 10 mg/kg as a training dose have shown that the NE reuptake inhibitor desipramine, which has not demonstrated abuse potential, substituted or partially substituted and bupropion fully substituted for cocaine (Nicholson et al. 2009; Paterson et al. 2010). Selective 5-HT reuptake inhibitors did not substitute for cocaine (Paterson et al. 2010; Terry et al. 1994).

In rhesus monkeys trained to discriminate cocaine, atomoxetine did not generalize to cocaine, whereas the indirect DA agonists GBR 12909 (vanoxerine), mazindol, nomifensine, and bupropion, each produced dose-related increases in cocaine-appropriate responding, with complete substitution for cocaine achieved at the highest doses of each drug (Kleven et al. 1990).

Similar results are also seen in squirrel monkeys. Atomoxetine produced some generalization at the lowest training dose of cocaine but this did not hold at higher doses of cocaine (Spealman 1995). Moreover, the pattern of responding for atomoxetine observed in the Spealman (1995) study was identical to the pattern observed for desipramine (which lacks abuse potential) and nisoxetine. Similar to cocaine, methamphetamine increases synaptic DA levels by blocking reuptake; in addition, methamphetamine can diffuse through the neuronal membrane and release cytoplasmic DA. In squirrel monkeys trained to discriminate methamphetamine (0.3 mg/kg, IM) from saline, a high dose of atomoxetine (17.8 mg/kg, IM) produced full substitution in 1 of 3 monkeys, whereas lower doses did not produce such an effect in any of the 3 monkeys (Tidey and Bergman 1998).

In summary, a review of animal drug discrimination studies indicates that atomoxetine will generalize to cocaine or methamphetamine under certain conditions, like NE reuptake inhibitors (e.g., imipramine and desipramine) lacking abuse potential. These antidepressants also generalize to the training drug under the same conditions that suggests the involvement of noradrenergic systems in these discrimination models. In monkeys, atomoxetine did not substitute for cocaine. Generalization to cocaine-like effects seems to occur when a low training dose of cocaine or a high dose of atomoxetine is used for testing, which substantially decreases response rates. The data demonstrating that atomoxetine, under some conditions, can generalize to cocaine does not directly imply abuse potential. Despite its different profiles of neurotransmitter effects in the drug discrimination studies, atomoxetine produces a pattern of effects similar to that of tricyclic antidepressants, drugs that have low abuse potential confirmed during many years of clinical use and availability. The nonclinical literature also documents a common subjective effect profile for abused stimulants that maps onto their abuse and dependence potential in man. In contrast, the nonclinical data in the area has distinguished atomoxetine from that of the abused stimulants, including methylphenidate. It was predicted from this distinction that atomoxetine would be devoid of psychomotor stimulant-like abuse and dependence potential and would therefore not be subject to drug diversion.

**Self-administration in monkeys** Atomoxetine was tested in two separate animal self-administration models that are predictive of abuse potential in humans. In the first study (Wee and Woolverton 2004), rhesus monkeys were prepared with chronic intravenous catheters and trained to press a lever to receive cocaine injections. Various doses of atomoxetine,
methylphenidate, desipramine, and their vehicles were periodically substituted for cocaine. A drug dose was considered a positive reinforcer in any monkey if the number of injections it maintained in all test sessions was outside the 95% confidence interval for all vehicle test sessions. Cocaine and methylphenidate clearly functioned as positive reinforcers, whereas atomoxetine and desipramine did not. The second study employed a choice paradigm (Gasior et al. 2005) in which rhesus monkeys were trained to press one lever for injections of either saline or drug, and another lever for the delivery of food. Dose–effect functions were determined for cocaine, methylphenidate, D-amphetamine, atomoxetine, and desipramine. Saline availability was typically associated with high rates of responding for food. In contrast, availability of cocaine, methylphenidate, or D-amphetamine at doses greater than 0.03 mg/kg/injection produced >90% responding on the injection lever. No dose of atomoxetine or desipramine maintained self-administration behavior on the injection lever until doses were increased to levels that disrupted overall behavioral functioning (Table 2) (Gasior et al. 2005). As such, these results from two different, well-controlled nonhuman primate self-administration models suggest that atomoxetine lacks abuse potential.

Human studies

The results from three abuse potential studies in humans provide valuable evidence to support the low drug abuse potential of atomoxetine compared with other stimulant drugs (summarized in Table 2). In the first study, physiological and subjective effects of atomoxetine and methylphenidate compared with placebo were assessed in a human laboratory study (Heil et al. 2002). Sixteen nondependent, light drug users (average age = 20 years) participated in six experimental sessions in which they received placebo, atomoxetine (20, 45, 90 mg) and methylphenidate (20, 40 mg) using a double-blind, Latin square design. Assessments were conducted before drug administration and at 30, 60, 90, 120, 150, 180, and 240 min after dosing. In addition to blood pressure (BP) and heart rate (HR), subjective drug effects were measured at each assessment using computer-based versions of Visual Analog Scales (VAS), the ARCI, and Adjective Rating Scales (ARS) (Heil et al. 2002).

The results of this study indicated that relatively few subjective drug effects of atomoxetine were different from the placebo (Heil et al. 2002). Specifically, the highest atomoxetine dose (90 mg) significantly increased the VAS “bad” and “sick” scores. Atomoxetine did not significantly affect scores on any of the ARCI subscales, except for a peak effect on the lysergic acid diethylamide subscale at the 90-mg dose. It could be argued that atomoxetine doses were too low to produce substantial subjective effects. However, doses were sufficiently high to demonstrate significant and to some extent unpleasant physiological effects. In contrast to atomoxetine, methylphenidate increased many self-report measures sensitive to stimulant effects, including the stimulant scales of the ARS, the VAS, and the ARCI benzedrine, amphetamine, and morphine–benzedrine subscales. Because this study of drug effects in humans demonstrated that atomoxetine did not engender pleasurable subjective effects, it provides evidence that atomoxetine is unlikely to have abuse potential.

In the second study, Lile et al. (2006) examined the discriminative stimulus and subjective effects of atomoxetine in six subjects with recent histories of stimulant use. After the subjects acquired the discrimination, they were given test doses of methylphenidate (5 to 30 mg), atomoxetine (15 to 90 mg), D-amphetamine (2.5 to 15 mg), triazolam (0.06 to 0.375 mg), and placebo. Subjective effects questionnaires (ARS, Stimulant-Sensitive Adjective Rating Scale, ARCI, and a locally developed Drug Effect Questionnaire) were administered at each assessment.
Questionnaire (DEQ), a performance task (Digit-Symbol Substitution Task), and cardiovascular evaluations were also completed. Methylphenidate and d-amphetamine increased drug-appropriate responding and produced stimulant-like subjective effects (e.g., increased ratings of “active/alert/energetic,” “stimulated,” “shaky,” and “jittery”) that were significantly different from placebo on all six domains of the DEQ. There was no significant difference between atomoxetine and placebo except for the DEQ domain “any effect” at the 90-mg dose, and for HR and BP effects attributable to noradrenergic activity. Only the 90-mg atomoxetine dose significantly increased methylphenidate-appropriate responding relative to placebo. Triazolam produced low, insignificant levels of drug-appropriate responding and sedative-like subjective effects. The authors suggest that the subjective effects profile of atomoxetine, partially overlapping with abused stimulants, and indicative of low abuse potential may mean that atomoxetine could be useful as a replacement therapy for stimulant abuse.

Lastly, in an inpatient study (Jasinski et al. 2008) that included 46 subjects with experienced, stimulant-prefering drug abuse history, examined the abuse potential of atomoxetine (Fig. 2). Subjects received double-blind, single doses of eight test drugs (placebo, 90 mg methylphenidate, 60 mg of the stimulant phentermine, 100 and 200 mg desipramine, and 45, 90, and 180 mg atomoxetine) using a balanced Latin square design. The Drug Rating Questionnaire-Subject (DRQS) and subscales of the ARCI data were collected for 24 h after each dose. Six-hour maximum scores were compared using analysis of variance. Methylphenidate and phentermine produced stimulant-like effects and euphoria, with significant scores on the DRQS “liking” subscale and the morphine-benzodrine, amphetamine, and benzedrine ARCI subscales. None of the doses of atomoxetine or desipramine produced stimulant-like effects or euphoria as measured by these scales. In this population of stimulant-prefering drug abusers, atomoxetine at doses up to 180 mg was not a euphoriant and did not produce stimulant-like subjective effects. Overall, the human laboratory studies strongly suggest a low abuse potential of atomoxetine.

Other human studies

To date, there are no studies evaluating the abuse potential of atomoxetine in patients with ADHD. However, atomoxetine treatment in a double-blind placebo-controlled trial in adult patients with ADHD and comorbid ethanol abuse/dependence, resulted in improvement in ADHD symptoms (Wilens et al. 2008b), which was significantly correlated with reduced alcohol cravings (Wilens et al. 2011). Further, the reduction in ADHD symptoms in the atomoxetine-treated group was not altered despite relapse to alcohol abuse. A post hoc analysis revealed that the cumulative heavy drinking days did not decrease until after ADHD symptoms improved and the adverse event profile was not suggestive of abuse potential for atomoxetine (Wilens et al. 2011).

Another approach is to study types of symptoms (e.g., dysphoria or depression, insomnia, irritability, frustration or anger, anxiety, and restlessness) immediately following discontinuation as to whether they suggest a drug withdrawal syndrome. Wernicke et al. (2004) evaluated the effects of abrupt discontinuation of atomoxetine in four placebo-controlled trials in children and adults with ADHD. Two of those were identical studies in children involved 9 weeks double-blind treatment followed by abrupt discontinuation or 1 week of single-blind placebo treatment. The other two were identical studies in adults involved 9–10 weeks double-blind treatment followed by a 4-week double-blind discontinuation phase where those on placebo continued on placebo and those on atomoxetine were randomized to either abrupt or tapered discontinuation. Atomoxetine was not associated with an acute discontinuation syndrome and hence, may be discontinued without risk of discontinuation-emergent adverse effects (Wernicke et al. 2004; http://pi.lilly.com/us/strattera-pi.pdf). The lack of discontinuation syndrome provides further supporting evidence for the low-abuse potential of atomoxetine.

Conclusions

The abuse potential evaluation for atomoxetine reviewed here was comprehensive and involved preclinical and clinical assessments including neuropharmaceutical characterization, receptor binding studies, animal behavioral studies (reinforcing effects, discriminative effects, physical dependence, and tolerance), and human pharmacology studies (subjective effects, toxicity and performance impairment, tolerance and physical dependence). Atomoxetine was not placed under CSA, which includes the US FDA’s eight-factor analysis of abuse potential for determination of control and scheduling of drugs prior to marketing. Atomoxetine was approved for the treatment of patients with ADHD as an uncontrolled and unscheduled medication in contrast to methylphenidate and amphetamine, which are placed under CSA and approved as schedule II (high physical or psychological dependence potential) drugs based on the eight-factor analysis.

Data from the in vitro and in vivo preclinical studies suggest that unlike stimulants (e.g., methylphenidate, amphetamines), atomoxetine does not have appreciable abuse potential. Further, atomoxetine was not associated with discontinuation-emergent adverse events in patients with ADHD in clinical trials that are suggestive of physical dependency.

Human abuse potential studies in atomoxetine were conducted in subjects with histories of substance abuse, which
is a standard procedure in the field. There is a growing body of literature examining medication diversion and misuse (Upadhyaya 2007; Wilens et al. 2008a). Evidence from those studies as well as from the postmarketing surveillance over the past 10 years has not indicated that atomoxetine is misused or diverted (Upadhyaya 2007; Wilens et al. 2008a).

Collectively, the broad experimental research summarized in this review supports that atomoxetine lacks abuse potential. As such, atomoxetine offers an alternative and efficacious nonstimulant treatment option for patients with ADHD.

Implications for future abuse potential research

It is evident that a comprehensive approach is needed for the evaluation of abuse potential of a psychoactive drug and that the results of a single study cannot be relied on to adequately characterize the potential for abuse. The eight-factor analysis conducted by the FDA seems like a reasonable first step that was able to predict lack of abuse potential with atomoxetine. Given that significant resources are required to conduct a program addressing the eight factors, more specific guidance, e.g., conditions under which such a program is needed, the type of required studies, animal models needed to be examined, types of comparators needed in human studies would be helpful.

Conflict of interest

Drs. Upadhyaya, Desaiiah, K. Schuh, Clarke, Durell, Trzepacz, Calligaro, Nisenbaum, Emmerson, and Allen are employees and shareholders of Eli Lilly and Company. Dr. L. Schuh is a former employee of Eli Lilly and Company and is currently affiliated with the St. Vincent Carmel Hospital, Carmel, IN. Mr. Bymaster and Dr. Kallman retired from Eli Lilly and Company and are currently affiliated with Indiana University, Indianapolis, IN, and Covance Laboratories, Greenfield, IN, respectively. Dr. Bickel received funding from Eli Lilly and Company in the past for his research. Frank P. Bymaster was an employee of the Eli Lilly and Company when the manuscript was initially written.

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