Atomoxetine Improved Response Inhibition in Adults with Attention Deficit/Hyperactivity Disorder

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Background: Atomoxetine, a highly selective noradrenaline reuptake inhibitor (SNRI), shows efficacy in the treatment of attention-deficit/hyperactivity disorder (ADHD). Compared with psychostimulants, atomoxetine has a distinct mode of brain action and potentially lower addictive potential. Studies have yet to assess whether atomoxetine improves cognition following a single oral dose in ADHD.

Methods: Twenty-two adults with DSM-IV ADHD were administered a single oral dose of atomoxetine (60 mg) in a placebo-controlled double-blind crossover design. Cognitive effects were assessed using stop-signal, sustained attention, spatial working memory, and set-shifting paradigms. Normative cognitive data from 20 healthy volunteers were collected for comparison.

Results: The ADHD patients under placebo conditions showed response inhibition and working memory deficits compared with healthy volunteers. Atomoxetine treatment in the ADHD patients was associated with shorter stop-signal reaction times and lower numbers of commission errors on the sustained attention task.

Conclusions: Atomoxetine improved inhibitory control, most likely via noradrenergically mediated augmentation of prefrontal cortex function. These results have implications for understanding the mechanisms by which atomoxetine exerts beneficial clinical effects and suggest novel treatment directions for other disorders of impulsivity.

Key Words: Attention, cognition, impulsivity, memory, stop-signal

Attention-deficit/hyperactivity disorder (ADHD) affects 3%–7% of children and is characterized by problems with impulsivity, inattention, and hyperactivity (1). At least 50% of these children still experience persisting symptoms into adulthood (2). Left untreated, ADHD has been linked to substance-related disorders, unemployment, patterns of unstable relationships, criminal offences, and driving accidents (3–5). Adults with the disorder also show increased prevalence of mood and personality disorders (3,6,7). Symptoms of ADHD are thought to be mediated by underlying dysregulation of frontostriatal circuitry and catecholamine neurotransmission, in particular implicating noradrenaline and dopamine (8–13). These abnormalities represent important treatment targets for optimizing everyday functioning and quality of life. Psychostimulants represent first-line pharmacologic treatment for the disorder and act to increase extracellular levels of noradrenaline and dopamine by preventing reuptake via transporter blockade and triggering release (14). These actions occur both cortically and subcortically (15,16).

The selective noradrenaline reuptake inhibitor (SNRI) atomoxetine shows efficacy in the treatment of ADHD (17–19) and represents the only licensed nonstimulant pharmacologic treatment currently available for the disorder (20). Atomoxetine may have several important clinical advantages over psychostimulants. Some 20%–30% of ADHD patients do not respond to adequate treatment trials using psychostimulants or are unable to tolerate them (2). Stimulants show abuse and addictive potential (21,22) and may in some cases worsen comorbid tics (23). By contrast, studies suggest that atomoxetine lacks midbrain dopamine effects and addictive properties (16,24) and shows efficacy in the treatment of comorbid tics (25,26). Atomoxetine may also be advantageous in patients with comorbid depression because it has antidepressive properties parsimonious with its classification as an SNRI (27,28); the presence of comorbid depression was predictive of superior response to atomoxetine treatment in adult ADHD patients (29). There may also be other clinical advantages that have been relatively underexplored. For example, atomoxetine treatment was associated with greater improvements in sleep quality compared with methylphenidate treatment in children with the disorder (30).

ADHD patients frequently show deficits on objective neuropsychologic tests dependent on the integrity of frontostriatal circuitry, including tests of response inhibition and working memory (12,31–36). These cognitive deficits have been shown to be ameliorated by administration of the psychostimulants methylphenidate and amphetamine (37–40). Thus, the objective measurement of cognition has proved useful in elucidating the mechanisms by which ADHD drugs are able to exert beneficial clinical effects. Despite growing clinical use worldwide, few studies have investigated the cognitive effects of atomoxetine in ADHD, and none of these examined short-term effects, which may prove useful for predicting clinical response and for guiding treatment choice (41,42).

In a study by Spencer and colleagues (43), 22 adults with ADHD were entered into a double-blind placebo-controlled crossover design with atomoxetine. Neuropsychologic assessment covered domains of inhibition (Stroop), sustained attention (auditory continuous performance), attentional set shifting (Wisconsin Card Sort), and visual memory (Rey–Osterrieth Complex Figures). Significant improvements were detected following 3-week atomoxetine treatment on the Stroop test alone, which the authors suggested was indicative of improvements in inhibitory capacity. Faraone and colleagues (44) consequently reported Stroop data from a large

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10-week double-blind placebo-controlled parallel study with atomoxetine. Improvements in Stroop performance were reported following atomoxetine treatment in adult ADHD patients with poor baseline performance. Some single-dose atomoxetine studies have been conducted in healthy volunteers and in experimental animals. The stop-signal paradigm measures the inhibition of prepotent responses ("response inhibition") and has been shown to be sensitive to ADHD, right inferior frontal gyrus pathology, and pharmacologic manipulations using psychostimulants and modafinil in ADHD (35,38,45,46). Chamberlain and colleagues (47) reported improved response inhibition on the stop-signal task following a single dose of atomoxetine (60 mg), compared with administration of placebo or the SSRI citalopram in healthy male volunteers (47). In rats, systemic dosing with atomoxetine improved inhibitory control on a rodent analogue of the stop-signal test (48) and reduced impulsive motor responses on the five-choice serial reaction time task (49).

The aim of our study was to evaluate the cognitive effects of acute atomoxetine treatment in adults with ADHD for the first time. Participants received 60 mg atomoxetine in a within-subject double-blind crossover design. Neurocognitive assessment focused on functions often reported to be dysfunctional in ADHD—namely, response inhibition, sustained attention, working memory, and attentional set shifting (34–36,50–52). The battery comprised objective theoretically validated computerized tests that had been used in prior acute methylphenidate and modafinil challenge studies in adults with ADHD (e.g., 38,50). Such tests show established sensitivity to frontostriatal integrity and can be used to draw comparisons between the neurocognitive effects of different pharmacologic agents. It was predicted, in light of the chronic studies discussed earlier, that atomoxetine would improve aspects of inhibitory control without significant effects on working memory or attentional set shifting.

Methods and Materials

All participants provided written informed consent. The study was approved by local research ethics committee (Cambridge, United Kingdom) and was formally exempted from clinical trials status by the Medicines and Healthcare Regulatory Agency (MHRA, London, United Kingdom). Twenty-two patients were recruited from a tertiary specialist referral center for the assessment and management of ADHD in adults. In addition to undertaking a comprehensive clinical assessment with a psychiatrist, questionnaires were completed by each patient, by an informant who had known the patient in childhood (usually a parent), and by an informant who had known the patient during the previous 6 months of adult life. Questionnaires included self-ratings and observer-ratings for the two sets of DSM-IV ADHD criteria, both in relation to the patient when aged 5–12 and in relation to adult behavior in the previous 6 months (53).

All patients received a DSM-IV diagnosis of ADHD using the following criteria: 1) DSM-IV ratings from an informant in relation to childhood features endorsing a specified minimum number (discussed later) of the nine criteria for predominantly inattentive type and/or of the nine criteria for the predominantly hyperactive–impulsive type (which consisted of three criteria for impulsivity and six for hyperactivity); 2) DSM-IV ratings by the patient and/or informant in relation to behavior during the previous 6 months endorsing a specified minimum number (corresponding to childhood endorsements, discussed later) of the nine criteria for predominantly inattentive type and/or predominantly hyperactive–impulsive type; 3) a judgment by a consultant psychiatrist specializing in the assessment and treatment of ADHD that the symptoms interfered significantly with everyday functioning and were not due to another disorder. Exclusion criteria were verbal IQ <90 (National Adult Reading Test [NART]) (54); contraindications for atomoxetine (e.g., history of renal or liver disease, www.bnf.org); significant motor or visual impairment that would interfere with neuropsychologic testing; neurologic disorder including tic spectrum or epilepsy; prior diagnosis of schizophrenia, psychotic disorders, or bipolar disorder; current major depressive disorder; and substance abuse in the last 2 months. Assessment of whether participants met these exclusion criteria was undertaken via clinical interview and examination of patients' hospital notes. We did not screen for or exclude patients on the basis of other comorbidities, including Axis 2 Cluster B personality traits, which are often found in this patient population (55). It was considered that exclusion of such comorbidities would be likely to produce a clinically unrepresentative sample. For the diagnosis of predominantly inattentive type, predominantly hyperactive–impulsive type, or combined type, a minimum number of six endorsed criteria were required for each of the relevant sets of nine DSM-IV criteria in both childhood and adulthood. For a diagnosis of ADHD in partial remission, the minimum number of endorsed DSM-IV criteria relating to recent behavior (but not in relation to childhood behavior, where it remained at six) was reduced to three for each of the nine criteria.

Two ADHD participants were excluded following nausea and vomiting approximately 30 min after capsule administration. These are known potential side effects of atomoxetine according to clinical trial data (17). The following descriptions and analyses refer to the remaining 20 participants. The ADHD subjects comprised 13 with combined type, six with inattentive type, and one with inattentive type in partial remission. Ten patients were ordinarily medicated on methylphenidate, one was ordinarily medicated on atomoxetine, and nine were not ordinarily receiving ADHD medication. The Global Severity Index (GSI) score from the Brief Symptom Inventory (56) in the ADHD patients was 1.28 ± .72 (mean ± SD), consistent with high prevalence of comorbidity expected in such patients (7,51). The total Attention-Deficit Scales for Adults (ADSA) score was 211.00 ± 13.46, consistent with ADHD diagnoses (57,58). The usually unmedicated and usually medicated patients did not differ from each other on ADHD symptom severity according to the ADSA (210.80 ± 14.72; 211.20 ± 12.96, respectively; analysis of variance [ANOVA] $p > .30$).

Participants were asked to abstain from alcohol and caffeine within 3 hours of study participation and not to take their usual ADHD medication (if they were receiving any) for at least 12 hours before participation on each occasion. It was felt that a longer washout period would have unduly affected everyday functioning for the volunteers. Subjects were entered into a randomized within-subjects double-blind placebo-controlled design and attended twice. Time between study visits was 8.0 ± 3.0 days (range 5–14 days). On each visit, atomoxetine (60 mg) or placebo was administered orally in blinded capsule form with water. This dose of atomoxetine was selected because it had previously yielded significant cognitive, neuroendocrine, and physiologic effects in healthy volunteers (47,59,60). Furthermore, unpleasant subjective feelings of "sickness" and "badness" increase considerably with larger acute doses (61).

After capsule ingestion, volunteers spent 1.5 hours resting in a quiet room before undertaking neuropsychologic tests taking approximately 2 hours. The timing of neuropsychologic assessment was based on pharmacokinetic data indicating peak plasma concentrations of atomoxetine approximately 1–2 hours following oral dosing (62) as well as prior studies (47,59,60). Tests are described

subsequently in the order in which they were administered. Cardiovascular measures (blood pressure and pulse) were also recorded using an automated hospital-grade sphygmomanometer at baseline and then 1.5 and 3.5 hours after capsule administration.

Twenty healthy control subjects were recruited from the local community to compare the neuropsychologic performance of ADHD patients on placebo and on atomoxetine with that of a normative sample. Exclusion criteria were current Axis I disorders or history of psychiatric or neurologic illness. These participants were tested on an identical neuropsychologic battery but were not entered into a pharmacologic trial (i.e, did not receive placebo or medication capsules). Psychopathology was screened out using the Mini International Neuropsychiatric Inventory (MINI) (63).

Neurocognitive testing comprised the stop-signal test (response inhibition) (45), Cambridge Neuropsychological Test Automated Battery (CANTAB) Rapid Visual Information Processing (RVIP) test (sustained attention) (64), three-dimensional intradimensional/extradimensional (3D IDED) test (cognitive flexibility) (50), and CANTAB Spatial Working memory test (65). The reader is referred to the supplementary online section for task descriptions.

Statistical Analysis

Effects of atomoxetine on cognition in the ADHD patients were investigated using repeated-measures ANOVA with drug condition (active or placebo) as the within-subject factor and order (active-placebo or placebo-active) as the between-subjects factor. Where significant effects of drug treatment on cognition were identified, effect sizes were calculated using Cohen's *D* (difference in mean between active and placebo conditions divided by the pooled standard deviation under active and placebo conditions). Data for ADHD patients on and off atomoxetine were also compared with those of healthy volunteers tested separately, using one-way ANOVAs. Cardiovascular effects of atomoxetine treatment were investigated using one-way ANOVAs. The conclusion of "lack of drug effect" is subject to type II error, whereas the presence of "drug effect" is subject to type I error (50,66). Taking this into consideration, $p < .05$ (two-tailed) was selected to indicate an effect and $p > .10$ as no effect. Because this was an exploratory study, *p* values were not adjusted for multiple comparisons.

Results

For the ADHD group, there were no significant differences in relevant demographic and clinical characteristics between those patients who received active treatment first and those who received placebo first (age, male:female ratio, NART IQ, GSI; all $p > .10$; see supplementary online table). Mean age in the ADHD and healthy control groups respectively were 31.60 ± 8.33 years and 30.90 ± 7.93 years. NART IQ in the ADHD and control groups respectively were 109.9 ± 9.2 and 112.1 ± 6.2. The two groups did not differ significantly from each other on these measures ($p > .10$). The male to female ratio was identical between ADHD and control groups (14 male subjects, 6 female subjects).

Cognitive Effects

Results from the neuropsychologic tasks are summarized in Table 1.

On the stop-signal test, there was a significant effect of drug treatment on stop-signal reaction times in the ADHD patients [$F(1,18) = 6.405$, $p = .021$]. This was because of the superior response inhibition when on drug (Figure 1, effect size Cohen's $D = .73$, medium-large). There were no significant effects of treatment order or drug by treatment order interactions (both *p*s > .10). The ADHD patients on placebo showed longer stop-signal reaction times than control subjects ($p < .01$) but did not differ from control subjects when they were on active treatment ($p > .10$). The beneficial effects of atomoxetine on response inhibition remained significant in a subsequent analysis of the subgroup of usually unmedicated patients alone ($p < .05$) and combined subtype patients alone ($p < .05$). Usually medi-

Table 1. Neuropsychological Performance of Adults with ADHD on and off Atomoxetine and Comparison with Healthy Control Subjects

	ADHD Patients ($n = 20$)				CS ($n = 20$)		Main Effect of Drug (Atx vs. Plc)[a]	Main Effect of Group (ADHD vs CS)[b]	
	Atx		Plc		Unt			Atx vs. Unt	Plc vs. Unt
Test and Measure	Mean	SD	Mean	SD	Mean	SD	*p*	*p*	*p*
Stop-signal									
SSRT (msec)	185.81	59.59	235.10	73.89	186.50	41.14	.021	.997	.009
Median go reaction time (msec)	440.55	65.91	422.35	55.33	421.35	79.43	.148	.411	.963
Go reaction time variability[c] (msec)	164.42	82.38	156.94	72.47	131.12	44.11	.742	.120	.173
P(inhib)	.47	.10	.49	.17	.55	.14	.758	.063	.234
Rapid Visual Information Processing									
Proportion of targets detection	.64	.20	.67	.26	.73	.19	.350	.164	.374
Commission errors	.80	.85	1.50	1.40	.85	1.31	.043	.886	.137
Spatial Working Memory									
Total between-search errors	18.85	15.20	22.65	13.33	11.70	11.36	.235	.031	.025
Strategy scores	32.95	6.28	32.15	5.26	29.55	6.24	.304	.058	.273
Three-dimensional set shifting									
Total errors	16.73	7.48	18.47	9.29	20.88	9.83	.432	.142	.432
Total reversal errors	6.16	3.00	7.47	6.75	5.51	3.49	.380	.536	.256
Extra-dimensional shift errors	8.80	7.61	9.37	9.41	12.27	9.57	.456	.210	.339

CS, control subjects; Atx, 60 mg atomoxetine; Plc, placebo; Unt, separately tested untreated control subjects.

[a]Repeated-measures analysis of variance, $df = 1,18$. For those tests for which significant effects of drug were identified, there were no significant effects of order or order by drug interactions (all *p*s > .10).

[b]One-way analysis of variance, $df = 1,38$.

[c]Within-subject standard deviation of the go response time.

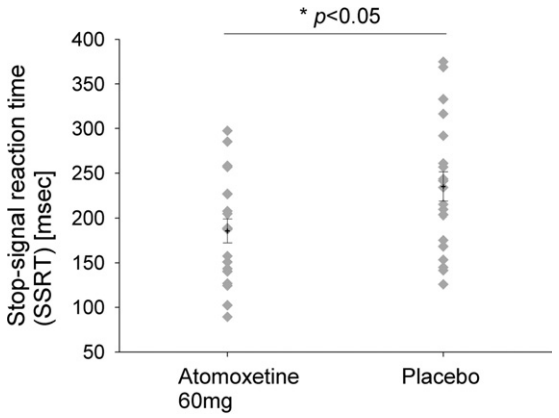

Figure 1. Effects of atomoxetine on stop-signal reaction time performance in adults with ADHD. Individual data (gray) and mean ± SEM (black).

cated and usually unmedicated patients did not differ significantly from each other on the response inhibition measure, whether on or off atomoxetine (all $p > .05$). There were no significant effects of drug on median reaction times or variability in reaction times in the patients nor did patients differ significantly from control subjects on these measures (all $ps > .10$).

On the CANTAB RVIP test, there was a significant effect of drug in the ADHD group on the number of commission errors made [$F(1,18) = 4.717$, $p = .043$]. This was due to fewer impulsive errors of commission being made when on active treatment (effect size Cohen's $D = .60$, medium). There was no effect of order and no significant drug treatment by order interaction (both $ps > .10$). The beneficial effects of atomoxetine on commission errors remained significant in a subsequent analysis in the subgroup of usually unmedicated patients alone ($p < .05$); however, these effects did not obtain significance in the combined subtype patients alone ($p > .10$). Usually medicated and usually unmedicated patients did not differ significantly from each other on this measure, whether on or off atomoxetine (all $ps > .05$).

There was no significant difference between ADHD patients (whether on atomoxetine or placebo) and control subjects in terms of commission errors (both $ps > .10$). There were no significant effects of drug on the proportion of targets successfully detected in ADHD patients ($p > .10$) nor did patients differ from control subjects on this measure (whether on atomoxetine or placebo; $p > .10$).

On the other tests, no significant effects of drug on dependent variables were found in the ADHD patients (all $ps > .10$). Compared with control subjects, ADHD patients whether on placebo or atomoxetine showed increased numbers of between-search errors on the CANTAB Spatial Working Memory test (both $ps < .05$). Patients did not differ significantly from control subjects in terms of 3D IDED set-shift task performance ($p > .10$).

Cardiovascular Effects

Cardiovascular parameters under atomoxetine and placebo conditions for the ADHD patients are shown in Figure 2. It can be seen that the only significant effect of atomoxetine treatment was increased pulse rate 1.5 hours after dosing ($p < .01$; other ps all $> .10$).

Discussion

Problems with impulsive behavior are implicated in the symptoms of ADHD and represent an important target for pharmacologic intervention (13). Impulsivity is a nonunitary construct in psychiatry (67–69). One aspect of impulsivity relates to the ability to suppress or inhibit inappropriate motor responses, and adult patients with ADHD frequently show deficits in response inhibition according to direct neuropsychologic assessment (34,70). The main finding of our study was that a single oral dose of atomoxetine improved aspects of inhibitory control (stop-signal reaction times, stop-signal task; commission errors, sustained attention task) in adults with ADHD. Patients on placebo showed deficits in response inhibition (stop-signal task) and working memory (CANTAB Spatial Working Memory task) compared with the control subjects. When on atomoxetine, ADHD patients no longer showed deficits in stop-signal response inhibition, although the working memory deficit remained. Impaired stop-signal and working memory performance in the ADHD patients under placebo conditions versus control subjects is largely consistent with prior studies using these tasks (e.g, 38,50–52,71). Intact flexibility on the 3D IDED test is consistent with a prior study using the same version of this paradigm (50). Atomoxetine was associated with a transient increase in pulse rate versus placebo 1.5 hours after oral dosing. No other cardiovascular effects achieved significance. In longer-term trials, atomoxetine has also been associated with increases in pulse rates, although it has been suggested that this is of minimal clinical significance (72).

These effects of atomoxetine on response inhibition parallel recent data from experimental animals showing that short-term administration of atomoxetine reduced impulsive responses on the rat five-choice serial reaction time test (49) and improved stop-signal reaction times on the rat stop-signal paradigm (48). In healthy volunteers, atomoxetine at the same dose also improved stop-signal response inhibition in healthy male volunteers, albeit there were no detectable effects on RVIP performance, perhaps because of ceiling effects (47). It is interesting to note that modafinil has also been shown to exert similar beneficial effects on stop-signal response inhibition in patients with ADHD (50) compared with healthy volunteers (73). These data suggest that proof-of-concept healthy volunteer studies can help to identify agents likely to improve inhibitory control in clinical contexts, with implications for novel drug development. The possibility of cognitive enhancement in people without neuropsychiatric disorders using ADHD medications raises important ethical and legislative issues (74). Some U.S. school districts already report that the proportion of males taking methylphenidate exceeds even the highest estimates of ADHD prevalence, making it likely that medications are being used to improve scholastic performance (75,76). Other ADHD medications, such as modafinil and atomoxetine, may show increasing use in such contexts.

Caution is required when comparing results among studies that have differed in the precise cognitive paradigms employed. Nonetheless, chronic atomoxetine treatment was previously associated with improvements on Stroop inhibitory measures in the absence of improvements on cognitive flexibility (Wisconsin Card Sort test) and memory (Rey–Osterrieth Complex Figures test) (43,44). These data resonate with those of our single-dose study, which found stop-signal response inhibition improvements in the absence of significant effects on cognitive flexibility and memory (ID/ED set shift and CANTAB Spatial Working Memory tests). Previously, however, chronic atomoxetine treatment was not associated with improvements on a continuous performance task (43), whereas we found reductions in commission errors on such a task. This disparity could be attributable to differences in the paradigms deployed; for example, we used a visual continuous performance task whereas Faraone and colleagues used an auditory task (44).

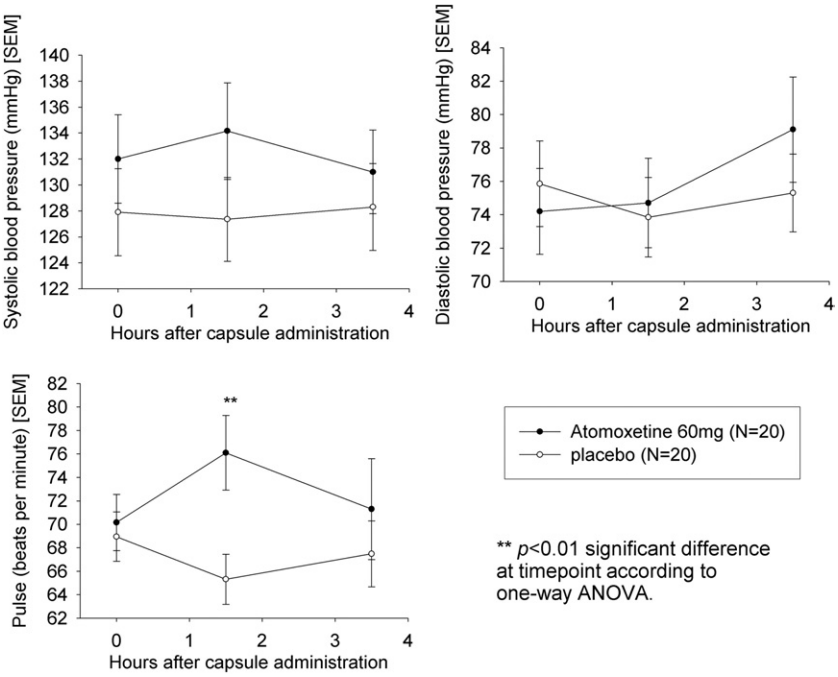

Figure 2. Effects of atomoxetine on cardiovascular parameters in adults with ADHD.

Atomoxetine had no effect on the CANTAB Spatial Working Memory test in ADHD patients, whereas a substantial body of research shows that noradrenaline manipulations in animals can affect component processes of working memory (11,77). It seems likely that this relates to the exact nature of the task: CANTAB Spatial Working Memory is a self-ordered search task that requires manipulation of information in working memory and strategy implementation. This task has established sensitivity to dopaminergic interventions including sulpiride (D2 receptor antagonist) (78,79). Arnsten and colleagues' (11,77) data showing noradrenaline effects on working memory mainly pertain to delayed response tasks that emphasize the maintenance of information in working memory. Subsequent atomoxetine studies in humans may thus benefit from using tests more reliant on maintenance such as a delayed-matching-to-sample task.

Increased intrasubject variability has been widely reported across several neuropsychologic tasks in children with ADHD (80). Adults may differ, however, because patients in this study did not show increased intrasubject variability on go reaction times on the stop-signal task. In a prior study in adult patients, variability was also not significantly different from control subjects, nor was there an effect of modafinil on this measure (50).

Atomoxetine selectively increases catecholamine neurotransmission (noradrenaline and dopamine*) in the prefrontal cortex, without the associated effects of psychostimulants on striatal dopamine transmission (16). In patients with neurosurgical lesions, volume loss within the right inferior frontal gyrus has been shown to correlate with magnitude of stop-signal impairment (45). Functional abnormalities in this region have been detected on a test of response inhibition in medication-naïve adolescents with ADHD (82). Therefore, the right inferior frontal gyrus represents a candidate neural substrate for the beneficial effects of atomoxetine on response inhibition. Subcortical regions, namely, the caudate and subthalamic nucleus, have also been implicated in response inhibition (83–85). It is believed to be less likely that atomoxetine acted directly at these sites given the previously noted animal research, although the right inferior frontal gyrus may exert top-down influences on lower brain structures (85). Pharmaco-functional magnetic resonance imaging could be used to investigate the precise effects of atomoxetine on neural circuitry during response inhibition in future work (86). Sustained attention shows some overlap with response inhibition in terms of underlying neural circuitry, being dependent on a right-lateralized frontoparietal network including the right inferior frontal gyrus (87–91). Noradrenaline has traditionally been linked to arousal and attention per se (92,93). Although the effects of atomoxetine on stop-signal reaction times and commission errors on the RVIP task could stem from common effects on arousal or sustained attention, no improvements were noted on the primary measure of sustained attention (RVIP target detection) in this study, rendering this explanation unlikely.

With regard to the precise differential involvement of noradrenaline and dopamine in impulse control, a prior study provided evidence that desipramine (a selective noradrenaline reuptake inhibitor with lesser specificity than atomoxetine) improved response inhibition in children with ADHD but that L-DOPA (which targets dopamine transmission) did not (94). Furthermore, Swann and colleagues (95) found that administration of the alpha-2 adrenoceptor antagonist yohimbine increased measures of impulsivity (using a continuous performance task) in healthy volunteers; similar findings were reported in animals (96,97). In the rat stop-signal paradigm, modafinil and methylphenidate improved response inhibition, and these behavioral effects were not blocked by concurrent administration of a dopamine receptor antagonist (98). Thus, the findings to date implicate noradrenaline in the modulation of response inhibition. This does not rule out the possible involvement of other neurochemical systems in response inhibition, nor the existence of functional interactions between such systems. Further clarification of the neurochemical substrates of atomoxetine's effects on cognition could be addressed using sampling of peripheral markers thought to reflect central noradrenaline function (e.g,

*The dual effects of atomoxetine on free frontocortical noradrenaline and dopamine levels are likely due to the low density of dopamine transporters in this region leading to dopamine "hitchhiking" via the noradrenaline reuptake transporter. See 81.

cortisol, alpha-amylase) (60,99) and translational models such as the rat stop-signal paradigm.

Limitations

The cognitive effects of atomoxetine were significant and clinically meaningful, with effect sizes in the medium to large range. A limitation of this exploratory study is that the data were not corrected for multiple comparisons. Therefore, the results should be regarded as preliminary and in need of replication in future studies to rule out type I error. Participants in this study were principally male patients with combined type ADHD—the most common form in adults (7). This study was not designed to assess differential cognitive profiles of ADHD subgroups or the differential impact of medication as a function of ADHD subgroup type, nor was it designed to investigate differential atomoxetine effects in usually medicated and usually unmedicated patients. Nonetheless, additional exploratory statistical analyses were undertaken. These showed that the beneficial effects of atomoxetine on response inhibition (stop-signal reaction times; commission errors on RVIP) remained significant in the usually unmedicated patients alone; furthermore, usually medicated and usually unmedicated patients did not differ from each other on these measures. The beneficial effects of atomoxetine on stop-signal reaction times also remained significant in an analysis of the combined-type patients alone, although the effects on RVIP were no longer significant, most likely because of the smaller effect size on this variable.

Comorbidity is the norm rather than the exception in adults with ADHD, with up to 80% of patients meeting criteria for at least one other Axis I disorder. The most frequently reported comorbidities include mood disorders (19%–37% of patients), anxiety disorders (25%–50%), personality disorders (10%–20%), and alcohol or substance abuse (10%–53%) (100). Family studies indicate that ADHD and these disorders are likely to share common etiologic underpinnings (101,102). In this study, we excluded patients with current major depression or substance abuse and those with certain prior diagnoses (schizophrenia, psychosis, bipolar disorder). We did not institute more stringent criteria because we believed this would result in a clinically unrepresentative sample. Therefore, many of the patients would have met DSM-IV criteria for one or more comorbidities (besides those excluded as discussed earlier), consistent with the raised global severity index scores demonstrated by this group. Although it is possible that comorbidities contributed to the neuropsychologic profile of patients versus control subjects, prior work suggests that cognitive deficits in adult ADHD remain robust even after taking comorbidities into consideration (103,104). It may also be that cognitive or clinical responses (or both) to atomoxetine are influenced by the precise ADHD type being examined and by comorbidities (e.g, 29), which may limit the extent to which the current findings can be generalized.

Participants were asked to abstain from usual medications for at least 12 hours before taking part in the study to minimize carryover effects of therapeutic medication on cognitive function. Longer washout was avoided to avoid unduly affecting patients' everyday function. Another potential limitation is that the stop-signal task was the only neuropsychologic measure for which we acquired sufficient numbers of rapid reaction times to allow for meaningful analysis of dispersion.

Conclusion

A single oral dose of atomoxetine was associated with improvements in inhibitory control in adult patients with ADHD. Future studies should investigate whether cognitive response to short-term atomoxetine dosing in ADHD patients is predictive of long-term clinical outcomes. We propose that atomoxetine exerts its beneficial clinical effects, in part, via noradrenergically mediated enhancement of inhibitory control. Unlike psychostimulants, atomoxetine appears to lack addictive potential and may have other clinical advantages in terms of sleep and the treatment of comorbidities such as depression. It would be of interest to assess the effects of atomoxetine on cognition and clinical symptoms in other conditions associated with difficulty suppressing inappropriate behavior such as trichotillomania, Tourette's syndrome, and Cluster B personality disorders, whether they occur comorbid with ADHD or separately (25,26,105).

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TWR, BJS, LC, and SRC consult for Cambridge Cognition. TWR consults for and UM has received speaker honoraria from Eli Lilly. The other authors report no competing interests.

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