EXPERT OPINION

Sofinicline: a novel nicotinic acetylcholine receptor agonist in the treatment of attention-deficit/hyperactivity disorder

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Introduction: Psychostimulants are first-line treatments for attention-deficit/hyperactivity disorder (ADHD), but their tolerability profiles and individual response variability fuel a continuing search for alternative medications. The observation that nicotinic agents improve cognition has led pharmaceutical companies to explore the potential utility of agonists of the nicotinic acetylcholine receptor (nAChR) system for ADHD treatments.

Areas covered: This article reviews Phase I and Phase II trials of sofinicline (ABT-894), an agonist of the nAChR $\alpha 4\beta 2$ subtype, as a potential non-stimulant treatment for ADHD. This includes one Phase II trial that compared sofinicline with atomoxetine, a noradrenergic reuptake inhibitor currently approved as a non-stimulant ADHD treatment. This article also reviews the chemistry, pharmacodynamics and pharmacokinetics of sofinicline.

Expert opinion: Sofinicline appears to be well tolerated and showing efficacy similar to that of atomoxetine. Although the number of patients studied to date is small, further evaluation of sofinicline in Phase II, and possibly Phase III, trials appears to be warranted. Additional studies are needed to explore the efficacy and tolerability of sofinicline with respect to: i) optimal dosing; ii) its use in combination with other medications for ADHD; and iii) its use in children and adolescents, who more commonly experience adverse effects when taking psychostimulant medications.

Keywords: attention-deficit/hyperactivity disorder, nicotinic agonist, non-stimulant, sofinicline

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1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is the most common psychiatric disorder of childhood, with an estimated prevalence of 8 – 10% of school-age children [1]. ADHD is also increasingly being recognized and treated in adults, with a prevalence estimated at 4.4% in the US [2] and 3.4% in other developed countries [3].

Current guidelines recommend that pharmacotherapy for ADHD should begin with a psychostimulant [4]. However, stimulant medications are ineffective in 10 – 30% of patients [5-7]. In addition, adverse effects (e.g., appetite suppression, tics or irritability) often limit dosing or the duration of treatment [8]. Moreover, concerns about abuse or inappropriate use of stimulants – particularly among young adults – can lead clinicians to discontinue them or to avoid prescribing them despite their efficacy [9]. As a result, under-treatment of ADHD is a substantial problem: Charach and Fernandez [10] have reported that as many as 50% of children and adolescents with ADHD discontinue or interrupt treatment after 1 year.

Second-line agents approved by the US FDA for the treatment of ADHD are commonly grouped together as 'non-stimulants'. This group includes the selective norepinephrine reuptake inhibitor atomoxetine as well as long-acting formulations

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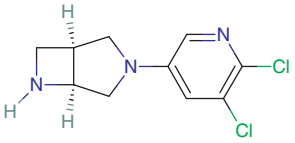
Box 1. Drug summary.

Drug name	Sofinicline
Phase	II
Indication	Attention-deficit/hyperactivity disorder
Pharmacological description	Selective agonist of the α4-β2 nicotinic acetylcholine receptor
Route of administration	Oral
Chemical structure	
Pivotal trial(s)	[38]

of two agonists of the central α-2 adrenergic receptor – typically referred to simply as α agonists – guanfacine and clonidine. These three medications are typically well tolerated but, on average, less effective than stimulants [5]. Third-line, off-label, treatment options include bupropion (a dopamine reuptake inhibitor) and tricyclic antidepressants. These latter agents are also demonstrably less effective than the stimulants [11-14]. Given the weaknesses of currently available treatments, there is a need for novel treatment options for ADHD.

An expanding understanding of the etiology of ADHD is facilitating the development of novel treatments. ADHD was classically attributed to dysregulation of the catecholamine system because of the effectiveness of the stimulants and subsequent work elucidating dopaminergic pathways in the brain [15]. However, the procognitive effects of the cholinergic agonist nicotine, and early work in Alzheimer's disease, prompted the realization that the cholinergic system – specifically, activity mediated by the nicotinic acetylcholine receptor (nAChR) family – also influences cognition.

Modulation of neuronal nAChRs has been shown to impact both attention and memory [16]. Interestingly, work in animal models has shown that both agonists and antagonists of nAChRs can enhance various facets of cognition, including attention, set-shifting, learning and others [17-19]. The fact that agents that have opposing mechanisms of action can produce similar downstream effects underscores the complexity of cholingeric modulation of cognition.

Within this complex system, the two most predominant nAChR subtypes, which are also those most often implicated in cognition, are the α4β2 receptor and the α7 receptor. The $\alpha4\beta2$ subtype of the nAChR seems to be of particular importance in ADHD. Effects of cholinergic agonists on attention have been shown to be mediated by the $\alpha4\beta2$ subtype [20,21]. For example, isopronicline (also known as AZD-3480, Astra Zeneca), a partial $\alpha4\beta2$ receptor agonist, improved performance on the Cognitive Drug Research test battery in tasks evaluating attention [22,23]. Other partial nAChR agonists reduced distractibility in monkeys (ABT 418, ABT 089, Abbott Laboratories) [24].

This article reviews Phase I and Phase II trials of sofinicline (also known as ABT-894), an agonist of the nAChR $\alpha4\beta2$ subtype, as a potential treatment for ADHD (**Box 1**). Sofinicline differs from the nicotinic agents mentioned above because it is a full agonist and is selective for the $\alpha4\beta2$ receptor. This selectivity of sofinicline has generated hope that, in clinical trials, it might produce even greater improvements in cognition than those shown in previous studies with partial or nonselective agonists [25-29].

2. Overview of the market

The market for medications for ADHD, particularly the stimulant class, is large and growing. *Health Affairs* estimated that in 2003, the global market for long-acting stimulants was just over $1.5 billion [30]. By 2011, sales in the US market alone topped $7 billion [31]. For non-stimulants, in contrast, the global market in 2003 was ~ $250 million [30]. UpdatesPlus, a group that tracks drug development, estimated that the non-stimulant market was worth $600 million in 2012 [32]. The market analysis firm Datamonitor similarly projected that 'ABT-894 has the potential to achieve peak sales of between $400 m and $600 m' globally [33]. Driven by the possibility of entry into these markets, several agents are under development (**Table 1**).

3. Compound

Sofinicline is a selective agonist of the $\alpha4\beta2$ subtype of nAChR. It is under development by Abbott Laboratories in collaboration with NeuroSearch. It is currently produced as a capsule in doses of 1, 2 or 4 mg. It is a bicyclo-heptane; its chemical structure is 3-(5,6-dichloro-pyridin-3-yl)-1(S), 5(S)-3,6-diazabicyclo[3.2.0]heptane (**Box 1**) [34,35].

4. Pharmacodynamics

Sofinicline is a full agonist of the $\alpha4\beta2$ nAChR. It has high binding affinity, ~ 0.1 nM, for this receptor. The exact mechanism of action for sofinicline remains unknown. The $\alpha4\beta2$ receptor subtype is a ligand-gated ion channel, but there is some evidence to suggest that nicotinic receptor signaling may also affect second-messenger systems (e.g., Adams *et al.*, 2002, cited in [36]).

5. Pharmacokinetics and metabolism

Sofinicline is orally active and is metabolized hepatically. The serum half-life is 4 – 6 h. A sofinicline dose of 4 mg orally twice a day, at steady state, produced a C_{max} of 11 – 15 ng/ml [37]. For that dose, Bain *et al.* [38] reported a similar mean plasma concentration, 14.87 ng/ml, when measured within 6 h after the morning dose. T_{max} generally was reached within 2 – 4 h [38]. The absorption, bioavailability, active metabolites, volume

Table 1. Status of medications to treat ADHD currently in development.

Company	Name	Mechanism	Stage
Abbott Laboratories [38]	Sofinicline/ABT-894	Agonist of α4β2 nAChR	Phase II
Abbott Laboratories [25-28]	ABT-089	Agonist of α4β2 nAChR	Phase II
Alcobra, Ltd. [61,62]	MG-01C1	Antagonist of 5-HT_{2B} receptor	Phase III
Astra Zeneca [29]	AZD-3480	Partial agonist of α4β2 nAChR	Phase II
Durect/Orient Pharma [31,63]	ORADUR®	New formulation of methylphenidate	Phase III
Neurovance [64]	EB-1020	Dopamine/norepinephrine reuptake inhibitor	Phase II
P2D Bioscience [65,66]	PD-9475	Histamine autoreceptor agonist	Phase I
P2D Bioscience [65,66]	PD-2005	Dopamine transporter agonist	Phase II
Targacept [67]	TC-5619	Agonist of α7 nAChR	Phase II
CoMentis [68]	GTS-21	Mixed agonist/antagonist of α7 and α4β2 nAChR	Phase II

5-HT: 5-Hydroxytryptamine; ADHD: Attention-deficit/hyperactivity disorder; nAChR: Nicotinic acetylcholine receptor.

of distribution, extent of protein binding and excretion of the compound have not been reported.

6. Clinical efficacy

In animal models, sofinicline has improved both cognition and memory. Rueter *et al.* [39] reported that, in both rats and monkeys, pretreatment with sofinicline prevented or reduced the cognitive impairment induced by a subsequent injection of scopolamine. Rats that received sofinicline before scopolamine showed improved spatial memory, working memory and memory consolidation compared with rats that received only vehicle. In a similar experimental model, monkeys pre-treated with sofinicline showed improved short-term working memory.

Phase I studies have provided data on plasma drug levels arising from specific doses of sofinicline, as well as on its efficacy in animal models of inattention or other impairments in cognition. Investigators at Abbott Laboratories found that doses of sofinicline ranging from 1 mg daily to 6 mg twice daily yielded plasma drug levels of ~ 0.2 – 8 ng/ml in humans (Abbott unpublished data cited in [38]). These investigators report that a 2 mg daily dose of sofinicline yields unspecified procognitive effects at trough levels.

A single Phase II double-blind, randomized controlled trial has tested the efficacy of sofinicline in humans. Using a dose-finding, cross-over design, Bain *et al.* [38] randomized 243 adults with ADHD into five groups. Four groups received sofinicline at 1 mg daily, 2 mg daily, 4 mg daily and 4 mg twice daily. The fifth group received atomoxetine 40 mg twice daily. Response was measured as improvement in the total score of the Conners' Adult ADHD Rating Scale as rated by the investigator. In each group of participants, half received the active agent and half received placebo during an initial 4-week study period. All participants then underwent a 2-week washout period followed by 4 weeks of either placebo or active agent, whichever had not been received in the first study period. The investigators found a statistically significant improvement among patients receiving sofinicline 4 mg twice daily compared with placebo. The least squares mean difference in total symptoms between the group receiving sofinicline 4 mg twice daily and the placebo group was 6.69 ± 2.3 ($p = 0.006$). Patients receiving atomoxetine also showed significant improvement. The least squares mean difference in total symptoms between the atomoxetine group and the placebo group was 7.98 ± 2.65 ($p = 0.005$). Effect sizes compared with placebo were reported as $d = 0.45$ for sofinicline 4 mg twice daily and $d = 0.57$ for atomoxetine. No other dose of sofinicline led to statistically significant improvement.

7. Safety and tolerability

Overall, sofinicline has been well tolerated. Phase I data demonstrated that sofinicline at a dose of 6 mg twice daily produced a small but statistically significant increase in heart rate, averaging 3 beats/min (Abbott unpublished data cited in [38]). In the Phase II trial noted above, a similar and statistically significant increase in heart rate of 3.14 beats/min ($p < 0.05$) was noted for sofinicline at 4 mg daily compared with placebo; however, no such effect was found at a dose of 4 mg twice daily. The authors did not speculate on reasons for the variability in this observation. No deaths, serious adverse events or premature discontinuations were noted. The adverse events most commonly reported among participants who received sofinicline were nausea, dizziness, headache and fatigue [38].

8. Regulatory affairs

Sofinicline has been patented in the US and Europe. It has not yet been approved for the treatment of ADHD in any country. Abbott may be organizing a Phase II trial in a pediatric population [40]. As of the date of this writing, no Phase III trials of sofinicline have been registered [41,42].

9. Conclusion

Preclinical research has shown that pharmacologic intervention at the nAChR, particularly the $\alpha4\beta2$ subtype, can affect

working memory, attention and cognition. Sofinicline, a full agonist of the $\alpha 4\beta 2$ nAChR, has been shown to be effective in attenuating the cognitive deficits induced by scopolamine in rats and monkeys. In humans, at doses up to 6 mg twice daily, sofinicline has been safe, with only mild and relatively well tolerated side effects. One Phase II study has shown that sofinicline has efficacy superior to placebo and similar to that of atomoxetine for the treatment of ADHD in adults.

10. Expert opinion

Our understanding of the nAChR system as a target for the treatment of ADHD is maturing. Pre-clinical studies generated interest in the α4β2 subtype of the nAChR by showing impaired cognitive function in α4β2 knockout mice, and by showing that agonists of the neuronal nicotinic α4β2 receptor have procognitive effects [22,39,43,44]. Sofinicline is highly selective for the α4β2 nAChR and is a full, rather than partial, agonist. Existing Phase II research on sofinicline lends preliminary, although relatively weak, support to the benefits seen in animal studies, with tolerability similar to that of atomoxetine. While sofinicline does not appear superior to the existing non-stimulant treatment options for ADHD, it may eventually constitute an additional treatment choice, with a different mechanism of action and with side effects that seem to be both infrequent and mild.

It is important to note that there has been only a single Phase II trial of sofinicline, and it has limitations. First, although not noted by Bain *et al.*, it is relevant that treatment lasted only 4 weeks. Although the study was not designed to compare the efficacy of sofinicline to that of atomoxetine, many clinicians will, nonetheless, make an unconscious comparison of the two. In light of that fact, this relatively short duration may have minimized the efficacy of atomoxetine, and accordingly might have exaggerated the efficacy of sofinicline. This possibility is supported by the low effect size of atomoxetine found in this trial contrasted with effect sizes reported in many other trials of atomoxetine (0.70 – 1.3) [45-48], although not all (0.4 – 0.57) [49-51]. By comparison, the effect sizes of extended-release α agonists have been reported as 0.71 for clonidine [52] and 0.43 [53] to 0.86 [54] for guanfacine. Another limitation of this study is the dose of sofinicline that was used. The authors report that a dose of 6 mg twice daily led to an increase in heart rate of 3 beats/min. This is comparable, they note, to the heart rate effect reported for some stimulants, yet the authors do not clearly explain why a dose of 6 mg twice daily was not used in the trial. This may have led to an underestimate of the efficacy of sofinicline when dosed optimally. The authors of the study mentioned two additional limitations regarding tolerability. They note that data were collected on adverse events that were spontaneously reported rather than prospectively assessed and that the titration schedule of atomoxetine may have been rapid relative to that used in typical clinical practice. It is difficult to know whether the effect of the former limitation would favor or disfavor sofinicline. The latter limitation is likely to have led to an overestimate of the adverse effects of atomoxetine. These points may seem trivial, but when efficacy of a medication is weak, clinicians will pay greater heed to even a mild burden of side effects.

Further work is needed to justify Phase III trials of sofinicline. Questions remain about optimal, safe, efficacious dosing schedules for the drug and about its efficacy and effectiveness. It would be of interest to establish whether doses of sofinicline higher than 6 mg twice daily are safe, well tolerated and have procognitive effects greater than those reported with smaller doses. Because twice daily dosing is inconvenient and nearly all FDA-approved ADHD medications have extended-release formulations, the development of a longer-acting, once-daily formulation of sofinicline would be desirable. It would also be of interest to investigate the possible role of sofinicline in combination with other agents, rather than as a monotherapy for ADHD. Finally, it will be particularly important to assess the safety and efficacy of sofinicline in pediatric populations, because children prove intolerant of the stimulants' adverse effects more commonly than do adults, and because children constitute the largest pool of patients with ADHD.

Although manipulation of the α4β2 nAChR appears to hold potential for adjunctive treatment of ADHD, this potential is far from being realized. Nicotinic agonists developed by several pharmaceutical companies have shown weak efficacy compared to currently approved non-stimulant medications. This disappointment parallels a broader difficulty over the last several decades in achieving clinical success with nicotinic agonists for any psychiatric disorder [55].

The fundamental challenge to progress in ADHD treatment remains our incomplete understanding of the condition's pathophysiology at the genetic, molecular and network levels. Recent work in genetics shows that some individuals with ADHD have mutations in nAChR genes and that mutations in these and other genes may be so variable between populations that they impart more heterogeneity between cases of ADHD than previously suspected. The relationships of such mutations to nAChR activity, clinical disease and response to medication need to be better understood [56-60]. At the molecular level, the interplay between brain activity mediated by the α7 and the α4β2 receptors remains incompletely understood. In addition, the role of less common receptor subtypes such as α5 may need to be more fully elucidated. At the network level, a better understanding of the interactions of the cholinergic, glutamatergic and catecholaminergic systems is needed. A better understanding also of interactions within the cholinergic system may help to explain mysteries such as how it is that both agonists and antagonists of nAChRs can improve cognition. (See Hurst *et al.*, 2013 [55] for a fuller discussion of the molecular physiology of nicotinic receptors.)

As our understanding of the nuances of the nicotinic acetylcholine system improves, we anticipate that our ability to ameliorate patients' cognitive deficits will be gradually improved and refined. Until that time, however, because no

study has shown sofinicline or any similar agent to present a therapeutic advantage over the second-line drugs already in clinical use (atomoxetine, guanfacine, clonidine), it seems unlikely to find a secure market niche. If sofinicline survives Phase III testing, its role seems likely to be as an adjunct to stimulants or non-stimulants, or less probably, as a third-line treatment.

In summary, the investigation of nicotinic acetylcholine agonists in the treatment of ADHD and other cognitive disorders holds some promise as an avenue to expanding our understanding of the fundamental pathophysiology of ADHD. Nonetheless, it seems unlikely that many of the compounds in this class currently under development will achieve FDA approval.

Declaration of interest

JJ McGough has served on the advisory boards for Akili Interactive, Merck & Co. Sunovion, Theravance and Targacept and has received research support from Purdue and Shire Pharmaceuticals. Dr McGough contributed to research on sofinicline, which was published by Bain *et al.* in 2013 but did not receive any honorarium or any other financial support for their work on sofinicline. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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