Recent trends in ADHD pharmacotherapy: Do we need more divided attention?
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Table 1. DSM-IV Criteria for ADHD.

A. Either (i) or (ii):
   (i) Inattention: at least six of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:
   - often fails to give close attention to details or makes careless mistakes in schoolwork, work or other activities
   - often has difficulty sustaining attention in tasks or play activities
   - often does not seem to listen to what is being said to him/her
   - often does not follow through on instructions and fails to finish schoolwork, chores or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
   - often has difficulties organizing tasks and activities
   - often loses things necessary for tasks or activities (eg, school assignments, pencils, books, tools or toys)
   - is often easily distracted by extraneous stimuli
   - often forgetful in daily activities

   (ii) Hyperactivity-impulsivity: at least four of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:
   - Hyperactivity
     - often fidgets with hands or feet or squirms in seat
     - leaves seat in classroom or in other situations in which remaining seated is expected
     - often runs about or climbs excessively in situations where it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
     - often has difficulty playing or engaging in leisure activities quietly
   - Impulsivity
     - often blurts out answers to questions before the questions have been completed
     - often has difficulty waiting in lines or awaiting turn in games or group situations

B Onset no later than age 7.

C Symptoms must be present in two or more situations (eg, at school, work and at home).

D The disturbance causes clinically significant distress or impairment in social, academic or occupational functioning.

E Does not occur exclusively during the course of PDD, schizophrenia or other psychotic disorder, and is not better accounted for by mood, anxiety, dissociative or personality disorder.
activity in dopaminergic and noradrenergic pathways [16]. The majority of patients, to an extent including adults, will respond to one of the three broadly available (and as some say, overprescribed [17-19]) stimulants, methylphenidate [20], dextroamphetamine [21] and the mixed amphetamine salt drug, Adderall [22], or pemoline [23]. The tricyclic antidepressants, imipramine, desipramine and nortryptiline, which probably act through inhibition of norepinephrine reuptake are usually considered as second-line agents. Third-line agents include the atypical antidepressant, bupropion [24,25] and the α1-adrenoceptor agonist, clonidine [26] as a transdermal patch. Since excellent and extensive recent reviews are available on the subject [27,28], only the recent clinical development of chirally pure d-methylphenidate (the active isomer of the marketed racemic drug) by Celgene Corp shall be mentioned here. Once-daily oral and transdermal formulations of dl-methylphenidate have been developed by Alza Corp and Noven Pharmaceuticals, respectively. Because of their potential for abuse, psychostimulants are controlled drugs (Schedule II in the US), and their adverse effects may include precipitation of psychotic episodes [29]; they also induce weight loss, which may or may not be desirable. The cardiac side effect potential of tricyclic antidepressants is also well known. Developers have therefore been seeking ‘second uses’ of known antidepressants for ADHD. In collaboration with Chugai Lilly Clinical Research, Eli Lilly is investigating the mixed serotonin-norepinephrine reuptake inhibitor (SNRI), tomtoxetine (LY-135252, Figure 1). In a double-blind, placebo-controlled, crossover study of tomtoxetine in 22 adult patients [30], drug-specific improvement in ADHD symptoms was highly significant overall and sufficiently robust to be detectable in a parallel-groups comparison restricted to the first 3 weeks of the protocol. Of 21 patients showed improvement, especially in neuro-psychological measures of inhibitory capacity, after receiving tomtoxetine, compared with only 2 of 21 patients who improved after receiving placebo. Earlier open trials with the SNRI, venlafaxine (Wyeth-Ayerst; Figure 1), also yielded promising initial results [31], but development for ADHD was not undertaken because the drug may aggravate hyperactivity [32].

Figure 1.

Approaches that go beyond stimulant or antidepressant treatments are still sparse. A double-blind, placebo-controlled, 113-patient trial of Cephalon’s α1-adrenoceptor agonist, modafinil (marketed as Provigil for narcolepsy), showed no benefit in adults with ADHD. That nicotine improves attention has been known for such a long time that it is difficult to identify the original reports; in any case, this provides a strong rationale for the clinical investigation of neuronal nicotinic acetylcholine receptor modulators in ADHD. Recently published results from a double-blind pilot trial of Abbott’s pyrrolidinoisoxazole, ABT-418 (Figure 2), administered to 32 patients as a transdermal patch [33] showed significantly greater reduction in ADHD symptom checklist scores for the active drug (28% versus 15% for placebo). Symptoms reflective of attention, and subjects with less severe ADHD, responded more robustly to ABT-418. Dizziness and nausea were the most frequently reported adverse effects.

Figure 2.

Another interesting perspective concerns the histaminergic system [34], and in particular, antagonists at the presynaptic H1 receptor. It is the activation of this histamine receptor (by antihistamines seeking to target H1) that causes the drowsiness and diminished attention that is the unwelcome side effect for those medications. In contrast, H1 blockade in the CNS leads to increased histamine release and stimulation through release of acetylcholine, noradrenaline and dopamine. Corporate players in this still exclusive field include Schering, Glatech, which has GT-2331 (Perceptin; Figure 3) in phase II clinical trials, and Bioprojet. AMPA receptor modulators might also be beneficial in ADHD. Shire Pharmaceuticals is scheduled to evaluate Cortex’s AMPAkine, Cx-516, in the clinic.

Figure 3.

A subgroup of ADHD subjects has significantly lower proportions of plasma arachidonic acid and docosahexaenoic acid than controls. An ongoing double-blind study at Purdue University (West Lafayette, Indiana) is currently investigating the effect of nutritional long-chain polyunsaturated fatty acids in children with ADHD and symptoms indicative of essential fatty acids deficiency [35]. Are we now entering a new age of ADHD pharmacotherapy, almost a century after the condition was first described in 1902? The prospects are not bad. However, this brief overview shall not end without considering that a perspective that considers ADHD not entirely in terms of a defect concept might have some validity, and that “the word disorder puts the syndrome entirely in the domain of pathology, where it should not entirely be. Although [it] can generate a host of problems … high energy, intuitiveness, creativity, and enthusiasm … are completely overlooked by the ‘disorder’ model” [36]. It has been speculated that just as depression might be considered the downside of the unmatched emotional capabilities Homo sapiens enjoys ADHD might be the price it has to pay for its equally unique creativity [37].
References


