Amfetamine and methylphenidate medications for attention-deficit/hyperactivity disorder: complementary treatment options

Paul Hodgkins · Monica Shaw · David Coghill · Lily Hechtman

Received: 22 December 2011 / Accepted: 15 May 2012 / Published online: 5 July 2012
© The Author(s) 2012. This article is published with open access at Springerlink.com

Abstract  Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders among school-aged children. It is highly symptomatic and associated with significant impairment. This review examines the role of stimulant medications in the treatment of children and adolescents with ADHD. Published clinical studies that compared methylphenidate- and amfetamine-based stimulants in children and adolescents with ADHD support the therapeutic utility of stimulant treatments, and suggest robust efficacy and acceptable safety outcomes in groups treated with either stimulant. Evidence-based guidelines agree that each patient with ADHD is unique and individual treatment strategies that incorporate both drug and non-drug treatment options should be sought. In seeking to optimize individual response and outcomes to stimulant therapy, important considerations include the selection of stimulant class, the choice of long- or short-acting stimulant formulations, addressing effectively any emergent adverse effects and strategies aimed at enhancing adherence to dosing regimen and persistence on therapy.

Keywords  Amfetamine · ADHD · Central nervous system stimulants · Medication adherence · Methylphenidate

Abbreviations

ADHD Attention-deficit/hyperactivity disorder
AMF Amfetamine
CGI-I Clinical global impressions-improvements
CI Confidence interval
CPRS-R Conners’ Parent Rating Scale-Revised
CTRS Conners’ Teacher Rating Scale
CTRS-R Conners’ Teacher Rating Scale-Revised
d-AMF Dexamfetamine
5-HT 5-Hydroxytryptamine
IOWA Inattention/overactivity with aggression
LDX Lisdexamfetamine dimesylate
MAS Mixed amfetamine salts
MPH Methylphenidate
MTA Multimodal treatment study of children with ADHD
OROS MPH Osmotic release oral system methylphenidate
SD Standard deviation
SH Spontaneously hypertensive
SMD Standardized mean difference

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders among school-aged children, with a worldwide prevalence estimated to be
5.29% (95% confidence interval [CI], 5.01–5.56%), based on a meta-analysis of 102 studies incorporating more than 170,000 participants from all continents [79]. ADHD is a heterogeneous disorder that is, however, characterized by the core symptoms of inattention and hyperactivity/impulsivity [2]. ADHD results in significant impairment, and its treatment should address both the core symptoms and any comorbid conditions, behavioural or psychosocial impairments, and learning difficulties that may be present [17, 66, 75, 91].

This review examines the role of stimulant medications as part of a multimodal treatment strategy in children and adolescents with ADHD. The review first explores the place of stimulant medications in clinical treatment guidelines around the world and then briefly reviews the overlapping but distinct mechanisms of actions of the methylphenidate (MPH) and amphetamine (AMF) classes of stimulant in the pathophysiology of ADHD. Next, we provide an update of direct and indirect clinical comparisons of efficacy of these stimulants in the treatment of ADHD. Finally, we discuss the role of stimulants within a comprehensive strategy aimed at optimizing treatment for the benefit of an individual with ADHD and their family members or caregivers.

Treatment recommendations in clinical guidelines

Guidelines from around the world differ in their treatment recommendations [85]. There is, however, general agreement that a comprehensive, multimodal treatment plan should be developed by the clinician, patient and family working closely together. In this plan, psychoeducation, parent/caregiver management training, behavioural and educational intervention, and medications are balanced to create the optimum treatment paradigm for each individual with ADHD [1, 15, 17, 66, 75, 77, 91, 93]. Specific treatment plans will be based, in part, on problems and impairments identified for the child and on access to and funding of healthcare resources. These differ by jurisdiction and geography, both between and within different countries.

Considerable evidence has accumulated over several decades that most patients with ADHD symptoms can be successfully treated by psychopharmacotherapies [33, 61] as part of a comprehensive treatment approach. Short- and long-acting formulations of the stimulants MPH and AMF, including the recently introduced AMF prodrug lisdexamfetamine dimesylate (LDX), the selective noradrenaline reuptake inhibitor atomoxetine, and the ₃₅ adrenergic receptor agonists clonidine and guanfacine (including short- and long-acting formulations) are all approved by the US Food and Drug Administration (FDA). However, the range of ADHD medications available to patients and physicians is not as extensive in many countries outside North America. In the USA, the American Academy of Child and Adolescent Psychiatry Practice Parameters recommend that treatment plans consist of psychopharmacotherapy and/or behavioural therapy. The initial medication should be one of the following FDA-approved drugs: MPH, AMF, mixed amphetamine salts, or atomoxetine [1, 75, 77]. The American Academy of Pediatrics (AAP) recommends that pre-school children receive behavioural therapy, with MPH only prescribed if moderate-to-severe dysfunction remains. For school-aged children, the AAP recommends FDA-approved medications and/or behavioural therapy, and for adolescents recommends the use of medications and that behavioural therapy may be used. With regard to medications, the AAP considers the evidence of efficacy to be particularly strong for stimulants and less strong for atomoxetine, long-acting guanfacine and long-acting clonidine [1, 75, 77]. The noradrenaline and dopamine reuptake inhibitor bupropion and tricyclic antidepressants, including imipramine, are listed within US guidelines as medication options for ADHD, but are not approved [75]. In Australia, MPH and AMF are also both recommended as first-line treatments [93], and in Canada, long-acting preparations of MPH and AMF or atomoxetine are all considered to be the first-line treatments [17].

In European countries, pre-school children and school-age children with ADHD with moderate impairment, psychoeducation and behavioural intervention are generally recommended as first-line treatment. In cases of severe ADHD with severe impairment, of moderate impairment that has failed to respond to psychoeducation, and when behavioural interventions are unavailable, medication should be offered [66, 91]. MPH, in short- or long-acting formulations, is generally recommended as the first choice medication for ADHD in Europe. Atomoxetine, though generally less effective than stimulants, is also widely available and may be recommended as an alternative to MPH [9, 24, 57, 63, 66, 84, 91]. AMF formulations are less widely available, typically due to either not being approved by regulatory agencies or not being placed on national formularies. Unusually within Europe, both MPH and AMF classes of stimulant are approved in the UK and are covered in national guidelines. In England and Wales, treatment algorithms recommend MPH as the first-line medication for ADHD, with atomoxetine as a second-line option. Although short-acting AMF is approved for ADHD, the National Institute of Health and Clinical Excellence (NICE) considered that the published trials were not of good enough quality to be included in their review, and so AMF is recommended only when symptoms are unresponsive to the maximum tolerated dose of MPH or atomoxetine [66]. National recommendations are

© Springer
reflected by a marked imbalance in prescribing patterns for
the two classes of stimulant for the treatment of ADHD, the
numbers of prescriptions in England (2010 figures) for
MPH and AMF were 661,463 and 45,519, respectively
[65]. Even in Scotland, where short-acting AMF is con-
sidered as a potential second-line treatment, it is prescribed
disproportionately less frequently than MPH. In addition to
the stimulants and atomoxetine, clonidine, guanfacine,
bupropion, modafinil and tricyclic antidepressants are lis-
ted within European guidelines, but are not approved, as
medication options for ADHD [66, 91].

Long-acting stimulant formulations are as efficacious as
their short-acting counterparts. In a meta-analysis of 32
clinical studies in children and adolescents (mean ages
within studies ranged from 8 to 15 years), there was no
difference in effect sizes for dependent measures (stand-
ardized mean difference [SMD]; 95 % CI) observed for all
studies that investigated short-acting (0.99; 0.88–1.1) and
long-acting stimulants (0.95; 0.85–1.1) [38]. Long-acting
stimulants offer the advantages of not having to be taken
during the school day, thereby reducing stigma for the
patient and the logistical problems for the school of storing
and administering scheduled medications. In addition,
one-daily formulations result in enhanced compliance,
more consistent and extended coverage throughout the day,
and reduced abuse potential than short-acting formulations
[9, 75]. Short-acting stimulants have the advantages of
greater flexibility of dosing and lower cost. Guidelines
recommend that individual clinical choice will determine
whether long- or short-acting stimulant medications should
be used [9]. However, some guidelines (Canada) recom-
end the use of long acting stimulants as first line [17].

In vitro and in vivo pharmacologies of MPH and AMF

The aetiology of ADHD is complex, with multiple genetic
and non-genetic factors implicated [22, 41]. However,
recent evidence has converged to suggest that catechol-
amine neurotransmission is impaired in the brains of
patients with ADHD [6, 7, 13]. Furthermore, stimulants
and the non-stimulant atomoxetine increase synaptic cate-
cholamine concentrations in the brain, particularly in the
prefrontal cortex, although their precise mechanisms of
action differ (Fig. 1).

The primary molecular targets of MPH are plasma mem-
brane dopamine and noradrenaline transporters [60]. In vitro
experiments demonstrate that uptake of dopamine and nor-
adrenaline is inhibited by dl-threo-MPH with modest potency
(inhibition constant [Ki], 160–341 and 40–238 nM, respec-
vally) [49]. Intraperitoneal administration of dl-threo-MPH
10 mg/kg to spontaneously hypertensive rats elicits a
rapid 3–4-fold increase in extracellular concentrations of
noradrenaline in the prefrontal cortex and dopamine in the
striatum, peaking within 45 min of dosing, and remaining
above control levels for at least 3 h [48].

Like MPH, d-AMF inhibits uptake of dopamine and
noradrenaline with modest potency (Ki 34–225 and
39–55 nM, respectively). Unlike MPH, d-AMF also
inhibits 5-hydroxytryptamine (5-HT) uptake (Ki 1.4–3.8 μM)
[49]. d-AMF also induces the release of monoamines from
presynaptic terminals [49], possibly via mechanisms that
include an interaction with vesicular monoamine trans-
porter 2, and the reversal of plasma membrane monoamine
transporters [30, 52, 53, 82, 90]. Evidence of a weak
affinity for monoamine oxidase (Ki 20 μM) suggests that
d-AMF also inhibits the metabolism of monoamines [49].
Intraperitoneal administration of d-AMF 1 mg/kg to
spontaneously hypertensive rats elicits a 15-fold increase in
striatal dopamine concentrations 30 min post-dose that
return to control levels within 90 min, and a fourfold
increase in noradrenaline concentrations in the prefrontal

![Fig. 1 Overlapping but distinct putative mechanisms of action of a methylphenidate (MPH) and b amphetamine (AMF) at the dopamine synapse. VMAT2 vesicular monoamine transporter 2](image-url)
cortex within 45 min of dosing that remain above control levels for at least 3 h. Unlike MPH, d-AMF also elicits elevations in extracellular 5-HT concentrations in vivo [55].

**Clinical comparisons of MPH and AMF**

Table 1 presents a summary of the MPH- and AMF-based stimulants that are used in the treatment of ADHD. In clinical studies, the efficacy and side effects of a treatment in respect of a particular outcome measure may be assessed at the overall group mean or individual level (response rate). There are multiple methods for comparing the efficacy of ADHD medications. The strongest evidence is provided by direct, head-to-head, parallel-group studies. However, the paucity of such studies means that other clinical trial designs, including crossover studies and meta-analyses, must be used to compare efficacy across stimulant treatments.

**Search strategy for the identification of published clinical comparisons of MPH and AMF**

PubMed literature searches were conducted (in March 2011) for papers containing combinations of MPH-based

| Drug | Duration of action (h) | Composition | Duration of action (h) |
|------|------------------------|-------------|-----------------------|
| Adderall® (mixed salts of dl-AMF) | 4–6 [3] | Capsulated biphasic beads | 8–12 [3, 9, 17] |
| Dexedrine® (d-AMF sulphate) | 4–6 [3, 17] | Capsulated biphasic beads | 6–10 [3, 17] |
| DextroStat® (d-AMF sulphate) | 4–6 [3] | VyvanseTM (d-AMF) | 13–14 [17] |
| Focalin® (d-MPH) | 4 [3] | Biphentin® (racemic MPH) | 10–12 [17] |
| Concerta® (racemic MPH) | 4 [3, 62] | Osmotically controlled release | 8–12 [3, 9, 17, 62] |
| Daytrana® (racemic MPH) | 4 [3, 62] | Transdermal patch delivery system | 8–12 [3] |
| Equasyrm XL®/Medate CD® (racemic MPH) | 4 [3, 62] | Capsulated biphasic beads | 8 [3, 9, 62] |
| Focalin® XR (d-MPH) | 4 [3, 62] | Capsulated biphasic beads | 8–12 [3] |
| Metadate ER® (racemic MPH) | 4 [3, 62] | Wax matrix tablets | 8 [3, 62] |
| Medikinate® retard (racemic MPH) | 4 [3, 62] | Capsulated biphasic beads | 7–8 [3, 9] |
| Methylin® ER (racemic MPH) | 4 [3, 62] | Wax matrix tablets | 8 [3, 62] |
| Methylin® SR® (racemic MPH) | 4 [3, 62] | Wax matrix tablets | 8 [3] |
| Ritalin LA® (racemic MPH) | 4 [3, 62] | Capsulated biphasic beads | 8–10 [62] |
| Ritalin SR® (racemic MPH) | 4 [3, 62] | Wax matrix tablets | 8 [3, 62] |

**Table 1** Structure of amfetamine (AMF) and methylphenidate (MPH), and examples of commercial formulations used in the treatment of ADHD

---

ADHD attention-deficit/hyperactivity disorder, d-AMF dexamfetamine, dl-AMF racemic amfetamine, MPH methylphenidate

* Subdivided into intermediate and long-acting formulations by some authors [27, 75]
studies (search terms: methylphenidate, Biphentin, Concerta, Daytrana, Equasym, Focalin, Medikinet, Metadate, Methylin, Ritalin) and AMF-based studies (search terms: amphetamine, Adderall, Dextedrine, Dextrostat, lisdexamfetamine). Results were limited to ‘clinical trial’ but were not limited by publication date. A total of 176 references were identified, of which 150 had English language abstracts. Identified papers were filtered for relevance based on the content of their abstracts. Inclusion criteria for references were the reporting of clinical outcome data (not biochemical, cytotoxicological, or preclinical data), concerned with ADHD and its treatment (not drug abuse, drug abuse liability, or comorbid symptoms such as tics), reported randomized, double-blind, controlled trials (not open label or n-of-1 trials), and reported comparisons of MPH- and AMF-based stimulants (not pooled stimulant groups or studies in which one or other stimulant was a simple positive control).

Direct clinical comparisons of MPH and AMF

Head-to-head comparisons

The results of the search for published randomized clinical studies that directly compare MPH- and AMF-based stimulants are shown in Table 2. Of the 13 published studies that were identified, there was one parallel-group (i.e. head-to-head) study [76]. This study compared short-acting mixed AMF salts (MAS) with short-acting MPH in the treatment of 58 children with ADHD. As the result of a dose optimization protocol designed to arrive at the ideal balance between efficacy and side-effects, mean daily doses of short-acting MAS and MPH in the final week of the study were 12.5 and 25.2 mg, respectively. The mean daily inattention/overactivity factor of the Inattention/Overactivity with Aggression (IOWA) Conners’ Teacher Rating Scale (CTRS) in the MAS-treated group (mean 0.49) was statistically superior to that of the MPH-treated group (mean 0.81), and both were statistically superior to placebo (mean 1.49). Similarly, the aggression/defiance factor of the IOWA CTRS in the MAS group (mean 0.29) was statistically superior to the MPH group (mean 0.49), and both were statistically superior to placebo (mean 0.72). Further, patients treated with MAS were superior to MPH in the Clinical Global Impressions-Improvements (CGI-I) scale (means 1.6 and 2.35 for the MAS- and MPH-treated patients, respectively) and both were superior to placebo (mean 3.22). The proportion of responders (i.e. improvement in CGI-I scores of 1 or 2) also favoured MAS treatment (MAS 90 %, MPH 65 %, and placebo 27 %) [76]. As will be discussed later, there was no statistical difference in parent-reported side-effects of moderate or severe intensity at the end of the study. Thus, evidence from this parallel-group comparison suggests the superiority of short-acting AMF-over short-acting MPH-based stimulants at optimized daily doses. The authors acknowledged, however, that the dose-optimization algorithm employed, may have limited dosing in the methylphenidate group [76]. It is also possible that the group differences could be a consequence of the longer half-life, and subsequent longer duration of action, of the MAS preparation (up to 6 h) compared to the MPH preparation (up to 4 h).

Crossover studies

An advantage of crossover clinical trials is that the within-group design permits the comparison of the treatments in each individual patient, rather than at the group or population level only. A previous comparative review [4] of crossover studies of short-acting formulations of AMF and MPH found no consistent statistical differences in group means of outcome measures. Of a total of 174 patients in six crossover studies, 48 (28 %) responded better to AMF and 27 (16 %) responded better to MPH, and at least 72 (41 %) responded to both; in all studies except for one in which patients exhibited comorbid Tourette’s syndrome, there was a non-significant trend for superior response in patients treated with AMF over those treated with MPH [4].

Most of the crossover studies listed in Table 2 that compared the efficacy of MPH and AMF in patients with ADHD reported equivalence in outcome measures for the two classes of stimulant at the level of the group mean. Those studies that observed statistical superiority of one stimulant over the other for particular outcome measures are reviewed below.

Studies that reported outcomes that favoured MPH included an Australian study, in which 125 treatment-naïve children (aged 5–15 years) were randomly assigned to receive either MPH or AMF [31]. Doses were fixed and based on body weight (short-acting MPH 0.3 mg/kg twice daily; short-acting AMF 0.15 mg/kg twice daily). After 2 weeks of treatment, both stimulants induced significant improvements in baseline scores for all factors of the Conners’ Teacher Rating Scale-Revised (CTRS-R) and the Conners’ Parent Rating Scale-Revised (CPRS-R). In the CTRS-R, there was a statistically significant difference (MPH effect minus AMF effect) in favour of MPH in treatment-induced improvements in conduct problems (difference 3.31, 95 % CI 1.11–5.50, p < 0.01), hyperactivity factor (difference 2.78, 95 % CI 0.70–4.86, p < 0.01), inattentive-passive factor (difference 1.61, 95 % CI 0.30–2.92, p = 0.02) and hyperactivity index (difference 2.60, 95 % CI 0.69–4.51, p < 0.01). In the CPRS-R, the difference in improvement in favour of MPH reached statistical significance for the anxiety factor only.
| Reference            | Study design | n  | Mean age in years | Dose\(^a\)                                                                 | Efficacy                                                                                           | Tolerability                                                                                           | Response rate, n (%)                                                                 |
|----------------------|--------------|----|-------------------|----------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Winsberg et al. [99] | Crossover    | 18 | 8.5               | Adjusted daily doses: MPH, \(\leq 40\) mg d-AMF, \(\leq 60\) mg           | No difference in behavioural ratings between MPH and d-AMF                                         | Insomnia and appetite loss                                                                         | NR NR 14/18 (78) 11/18 (61) |
| Arnold et al. [5]    | Crossover    | 29 | 8                 | Adjusted mean daily doses: MPH, 1.25 mg/kg d-AMF, 0.63 mg/kg Caffeine, 12.1 mg/kg | Both MPH and d-AMF superior to placebo Non-significant trend for AMF to be superior to MPH in all measures | Appetite loss for both drugs Stomach aches reduced in d-AMF vs. placebo | 19/29 (66) 19/29 (66) 26/29 (90) 13/29 (45) |
| Borcherding et al. [12] | Crossover | 18 | 9.6               | Fixed escalating doses: MPH, 25–90 mg/day d-AMF, 10–45 mg/day               | MPH produced greater lowering of motor activity than d-AMF                                         |                                                                                                       | 14/18 (78) 6/18 (33) 15/18 (83) 5/18 (28) |
| Pelham et al. [72]   | Crossover    | 22 | 10.4              | Fixed daily doses: MPH, 20 mg Ritalin SR-20\(^{a}\), 20 mg Dextedrine Spansule\(^{b}\), 10 mg Pemoline, 56.25 mg | In the context of an intensive summer treatment programme, dextedrine spansule and pemoline consistently had the most beneficial effects | Slightly more adverse events for Dextedrine Spansule\(^{b}\) than MPH or Ritalin SR-20\(^{a}\) | NR NR 15/22 (68) NR |
| Elia et al. [35]     | Crossover    | 48 | 8.6               | Fixed escalating doses: MPH, 25–90 mg/day d-AMF, 10–45 mg/day               | MPH produced greater reductions in motor activity than d-AMF Considerable individual differences in responses between the drugs observed |                                                                                                       | 38/48 (79) 42/48 (88) 46/48 (96) 34/48 (71) |
| Elia et al. [36]     | Crossover    | 33 | 9.3               | Fixed escalating doses: MPH, 25–90 mg/day d-AMF, 10–45 mg/day               | Patients attempted more mathematics and reading tasks on either drug Percent correct for mathematics tasks improved for d-AMF only |                                                                                                       | NR NR NR NR |
| Efron et al. [31, 32]| Crossover    | 125| 8.7               | Fixed daily dose: MPH, 0.6 mg/kg d-AMF, 0.3 mg/kg                           | On Conners’ Teacher Rating Scale, response was superior for MPH for conduct problems and hyperactivity factors | d-AMF caused appetite loss Insomnia and negative emotional symptoms worse for AMF than MPH | 90/ (72) 85/ (68) 118/ (94) 58/ (46) |
| Reference                          | Study design | \(n\) | Mean age in years | Dose(s) | Efficacy                                                                 | Tolerability                                                                 | Response rate, \(n\) (%) |
|-----------------------------------|--------------|-------|-------------------|---------|--------------------------------------------------------------------------|----------------------------------------------------------------------------|----------------------------|
| Pelham, Aronoff et al. [68]       | Crossover    | 25    | 9.6               | Fixed daily doses: MPH, 10, 17.5 mg Adderall\(\textregistered\), 7.5, 12.5 mg | In the context of an intensive summer treatment programme, the tested doses of Adderall\(\textregistered\) produced greater improvement than those of Ritalin\(\textregistered\) on many measures of behaviour in social and classroom settings. The lower dose of Adderall\(\textregistered\) was comparable with the higher dose of Ritalin\(\textregistered\). Treatment recommendations: Adderall\(\textregistered\), 7.5 mg, 11/25; 15 mg, 2/25; Adderall\(\textregistered\), 7.5 mg or Ritalin\(\textregistered\) 10 mg, 3/25; Ritalin\(\textregistered\), 17.5 mg, 4/25, neither (i.e. intensive behavioural therapy only) | Averaged across all medication days, more evidence of loss of appetite and trouble sleeping for the high-dose Adderall\(\textregistered\) treatment | 16/25\(b\) (64) 7/25\(b\) (28) 21/25\(b\) (84) |
| Pelham, Gnagy et al. [69]         | Crossover    | 21    | 10.3              | Fixed daily doses: MPH, 0.9, 0.75, 0.3 mg/kg Adderall\(\textregistered\), 0.6, 0.45, 0.3 mg/kg | In the context of an intensive summer treatment programme, total daily dose of 0.3 mg/kg/day Adderall\(\textregistered\) equivalent to 0.6 mg/kg/day MPH in daily rates of behaviours in classroom and social settings. Treatment recommendations: MPH, 4/21, Adderall\(\textregistered\), 6/21, 6/21 either drug, 5/21 neither (i.e. intensive behavioural therapy only) | Reports of appetite loss and trouble sleeping for both drugs when administered in the afternoon | 10/21\(b\) (48) 12/21\(b\) (57) 16/21\(b\) (76) |
| Castellanos et al. [19]           | Crossover    | 45    | 8.7               | Fixed escalating daily doses: MPH, 25–90 mg d-AMF, 10–45 mg | MPH and d-AMF produced similar improvements in continuous performance test omission and commission errors | NR NR NR NR | |
| Sharp et al. [86]                 | Crossover    | 42    | 8.9               | Adjusted daily doses: MPH, 10–70 mg d-AMF, 5–30 mg | Mean beneficial effects of MPH and d-AMF similar for all ratings | Mean adverse effects of MPH and d-AMF similar | 26/32 \(81\) 27/32 \(84\) 31/32 \(97\) 22/32 \(69\) |
| Pliszka et al. [76]               | Parallel group | 58    | 8.1               | Adjusted mean daily doses: MPH, 25.2 mg Adderall\(\textregistered\), 12.5 mg | Classroom inattentive and oppositional symptoms and CGI-I: both MPH and AMF superior to placebo Adderall\(\textregistered\) significantly superior to MPH in teacher ratings and CGI-I Beneficial effects of Adderall\(\textregistered\) persisted longer than MPH | Neither drug affected weight Greater number of patients on Adderall\(\textregistered\) reporting stomach ache or sadness/tearfulness not significant after correction for multiple tests | 13/20 \(65\) 18/20 \(90\) NR NR |
In another study in which short-acting stimulant formulations of MPH 0.45–1.25 mg/kg and AMF 0.2–0.6 mg/kg were administered at breakfast and lunchtime to 18 boys (mean age 9.6 years), both stimulants significantly reduced motor activity (truncal activity counts per hour) compared with placebo, but the reduction was greater for MPH than for AMF between the hours of 11 a.m. and 1 p.m. [12].

A recent crossover study compared the effects of the long-acting stimulant formulations osmotic release oral system MPH (OROS MPH; maximum daily dose 72 mg) and extended-release MAS (maximum daily dose 30 mg) on neuropsychological functioning in adolescents with ADHD (n = 35; mean age 17.5 years) [98]. There were no significant differences between OROS MPH and extended-release MAS in any of the outcomes studied. However, OROS MPH, but not extended-release MAS, was statistically superior to placebo in distracter errors and distracter reaction time in the Go/No-Go test and in Recall Accuracy in the Delayed Matching-to-Sample test, perhaps reflecting greater than a twofold MPH to AMF dose-ratio than that considered to be equivalent [98, 101].

In contrast to the above results favouring MPH, responses to short-acting AMF (maximum daily dose 45 mg) were superior to short-acting MPH (maximum daily dose 90 mg) in a crossover study of classroom performance in boys aged 6–12 years with ADHD. Compared with placebo, both drugs produced statistically significant improvements in performance (percent correct responses) and number of problems attempted for reading tasks, and both drugs improved the number of attempted arithmetic problems. However, improved performance in arithmetic problems compared with placebo was statistically significant for AMF only (mean [standard deviation] percent correct: AMF 97.1 [4.6]; MPH 96.2 [5.6]; placebo 94.0 [7.9]) [36]. Again, the longer duration action of the amphetamine may have influenced these results.

Meta-analyses

Using standardized effect sizes, it is possible indirectly to compare efficacy outcomes for particular treatments across studies. Standardized mean difference (SMD) is one way of calculating effect size. For example, an SMD of 1 indicates that the mean outcomes in drug and placebo groups differ by 1 (pooled) standard deviation. In interpreting SMD values, an SMD of 0.2 is considered small, 0.5 is considered medium, and ≥0.8 is considered large [21] (Fig. 2).

A series of recent meta-analyses have examined effect sizes of various outcome measures in patients with ADHD of different ages treated with different ADHD medications [38–40]. In a meta-analysis of 32 double-blind, placebo-controlled trials in youths (aged 6–18 years) with ADHD,
meta-analysis regression found that effect sizes for non-stimulant medications (SMD = 0.57) were significantly smaller than for both short-acting (SMD = 0.99, F1,31 = 25, p < 0.0001) and long-acting stimulants (SMD = 0.95, F1,31 = 15, p < 0.0001) [38]. Although this analysis did not stratify stimulant therapies according to their MPH or AMF class, it is interesting to note that the largest effect sizes for both short-acting (MAS, SMD = 1.34) and long-acting (LDX, SMD = 1.52) stimulants were seen for AMF-based therapies. When effect sizes were compared across 23 randomized, controlled trials of 11 different short- and long-acting stimulants in children and adolescents with ADHD, robust drug effects were observed in all individual studies. Furthermore, across all of these studies, effect sizes for AMF products were significantly greater than for MPH products (SMD = 1.03 vs. 0.77, t19 = 2.5, p = 0.02). Regression analyses found that several study variables, including stimulant formulation (short-acting vs. long-acting), type of dosing (fixed vs. optimized), and study design (parallel vs. crossover), were not associated with SMD. It is, of course, possible that heterogeneity between study variables may have obscured possible associations between these variables and SMD. Nevertheless, three study design features were identified that they were associated with SMD (age, type of score [outcome or change], and rater [physician, parent, teacher, or patient]), but the finding that effect sizes for AMF were modestly greater than those for MPH held after correcting for these confounding variables [39]. Equivalence of dosing between AMF and MPH stimulants was not demonstrated. Using the method of numbers needed to treat, another way of comparing outcomes from different studies, the authors calculated that 2.0 patients were needed to be treated with AMF for each positive outcome for total ADHD symptoms compared with 2.6 patients for MPH [39]. Overall, these pooled analyses provide strong evidence for the efficacy of stimulant medications in ADHD, while one meta-analysis provides evidence of the greater efficacy of AMF-based drugs compared with MPH-based drugs in children and adolescents. Again, the longer duration action of short-acting AMF than short-acting MPH may have contributed to these results.

Summary of clinical comparisons

Overall, some individual studies have demonstrated superiority of MPH over AMF, some have found superiority of
AMF over MPH, and others have shown no differences between the two types of medications. When meta-analyses are performed summarizing all available evidence, the effect sizes observed with AMF are greater than those observed with MPH, although issues of comparable dosing and differences in the duration of action of short-acting stimulants should be taken into account when interpreting these data. However, given the currently available evidence, it has not been demonstrated that one stimulant is more efficacious than another at a population level; direct head-to-head studies would be required to establish this definitively.

Tolerability of stimulant medications

There is considerable overlap in the adverse event profiles of MPH- and AMF-based ADHD medications [46, 47]. In the parallel-group comparison of MPH and MAS in children with ADHD, the adverse events reported in more than 10% of patients in the MPH treatment group were tiredness, appetite loss, irritability, and anxiousness; in the MAS group they were stomach ache, irritability, negative emotion (sadness, tearfulness), appetite loss, tiredness, and headache [76]. The incidences of stomach ache and negative emotion were numerically greater in the MAS group than in the MPH group but the differences were not significant after applying the Bonferroni correction for multiple statistical tests [76].

In crossover studies, insomnia and appetite suppression were generally reported to be the most common adverse events for both classes of stimulant [46, 47]. The severities (but not frequencies) of insomnia, irritability, proneness to crying, anxiousness, sadness, unhappiness, and nightmares were all reported to be greater in children treated with AMF 0.15 mg/kg twice daily than with MPH 0.3 mg/kg twice daily [32]. The incidence of overall adverse events has been reported to be numerically greater in children receiving long-acting AMF 10 mg/day than in those receiving short-acting MPH 10 mg twice daily or long-acting MPH 20 mg/day [72]. Furthermore, in a comparison of the safety and tolerability of short-acting MPH 10 and 17.5 mg twice daily and MAS 7.5 and 12.5 mg twice daily, parent-rated incidences of moderate-to-severe (on average) trouble sleeping and loss of appetite were greater in high-dose, MAS-treated patients (trouble sleeping 12%, loss of appetite 24%) than in high-dose, MPH-treated patients (trouble sleeping 4%, loss of appetite 4%) [68]. Finally, over 3 weeks’ dosing, mean weight loss was significantly greater than placebo in girls treated with AMF (maximum dose 0.64 mg/kg twice daily, mean [standard deviation] change from baseline −1.1 kg [1.0 kg], p < 0.01) but not MPH (maximum dose 1.28 mg/kg twice daily, mean [standard deviation] change from baseline −0.4 kg [1.1 kg], not significant) [86].

In contrast, nervous habits and mannerisms have been reported as being more common in boys treated with MPH (maximum mean dose 2.5 mg/kg twice daily), but not AMF (maximum mean dose 1.3 mg/kg twice daily), than in those treated with placebo [35]. In addition, the incidence of stomach aches in children was lower with AMF (mean dose 18.5 mg/day), but not MPH (mean dose 37.9 mg/day), than with placebo [5].

Based on the reviewed studies, the adverse event profiles of the two classes of stimulants appear to be similar. Some studies suggest that the frequency and severity of adverse events may be somewhat greater with AMF than with MPH products when AMF is compared with MPH, whereas side effects with MPH may be more common than with AMF when both drugs are compared with placebo.

Optimizing medication for an individual

The aim of optimizing an individual’s medication strategy is to achieve the maximum reduction of symptoms, or even the remission of ADHD, without the appearance of intolerable side effects. While it used to be the case that improvement in symptoms was the primary goal of treatment, clinicians are increasingly seeking treatment strategies that result in remission of ADHD in an individual. By remission we mean the loss of diagnostic status, with minimal or no symptoms, and optimal functioning with minimal impairment [88]. The likelihood of the appearance of particular side effects differs between individuals and between each medication class [46, 47]. Evidence-based guidelines recognize that each patient is unique and that treatment strategies should be tailored to an individual’s situation, taking into account a broad range of factors including age, type of ADHD, comorbid symptoms, treatment history, and the attitudes of patients and parents/caregivers to ADHD medications. The initial selection of medication strategy for an individual requires consideration of the class of drug, dose and desired pharmacokinetic properties (including speed of onset and duration of action). Subsequent optimization of treatment involves ongoing assessment for adequate efficacy and remission of impairment, and monitoring and treating treatment-emergent adverse events and adherence to the agreed therapeutic regimen [1, 15, 17, 66, 75, 77, 91, 93].

Choice of stimulant class

Although group average responses to MPH and AMF in patients with ADHD are similar, individuals may respond
very differently to the two drugs. While approximately two-thirds of patients typically experience improvements in various symptom domains in response to a single stimulant, if patients with an unsatisfactory response try the alternative class of stimulant, the proportion of patients who respond to one of the drugs may be as high as 95% [4, 31]. Updated response data for studies directly comparing MPH- and AMF-based stimulants are presented in Table 2. Of eight studies containing data for MPH and AMF formulations, the proportion of responders was higher for AMF in four studies, higher for MPH in three studies, and were equivalent in one study. In the only head-to-head comparison of stimulants, 90% of patients responded to MAS, 65% responded to MPH, and 27% responded to placebo [76]. When numbers of responders for each stimulant were combined across studies, 226 of 318 patients (71%) responded to MPH and 216 (68%) responded to AMF, suggesting that there is no meaningful difference in numbers of responders for MPH and AMF in ADHD. However, the proportion of patients responding to either class of stimulant (287 of 316 patients 91%) was higher than those responding to each single stimulant. These analyses confirm previous assertions that non-response is uncommon when an individual is offered both a MPH and an AMF [35], and that responses to the two classes of stimulant, although similar in the overall ADHD population, does vary between individuals [4]. Differences in the metabolic pathways and mechanisms of action of MPH and AMF (see above), the genotype of an individual [44, 89] and the pathophysiology of their ADHD [26] may be important factors in determining an individual’s response to the different stimulant drugs. In terms of clinical practice, these differential response rates support clinical guidelines that recommend that MPH and AMF are equally valid first-choice medications for the treatment of ADHD, and that if the first-selected stimulant class proves to be unsatisfactory, then a stimulant from the second class should be tried [75, 77]. The selection of which stimulant class to start with may be aided by methods for identifying patient subgroups that may preferentially respond to medication, including pre-specified and post-hoc subgroup analyses of clinical data [11, 23, 28, 29, 54, 87]. However, there are well-accepted constraints of both a priori and post-hoc specification [8, 56, 74, 78]. These limitations are starting to be addressed by the development of personalized treatment selection techniques; these combine patient characteristics from clinical trial data to form a risk score and then performing analyses on subgroups using a two-stage process that allows for treatment responses at an individual level to be made [16, 94, 102]. These methodologies have the advantage that they can systematically use multivariate regression models to select and combine multiple baseline covariates from different levels of analysis to define subgroups. With a view to the future, pharmacogenomics and non-genetic biomarkers may assist in the optimization and individualization of ADHD pharmacotherapy, although this is not yet possible [10, 19, 34, 44, 50, 89].

Choice of stimulant formulation

Reductions in the symptoms of ADHD by stimulants depend upon achieving sufficient occupancy of their molecular target(s) in the brain [95]. Positron emission studies suggest that peak occupancy of the dopamine transporter is reached approximately 60 min after oral dosing with short-acting MPH [96]. However, the elimination half-life of short-acting MPH is reported to be approximately 3 h [51] and of AMF to be approximately 7 h [14]. Therefore, two or, in the case of short-acting MPH, three daily doses are necessary to maintain therapeutic concentrations of stimulants within the brain throughout the day. For children and adolescents, repeat dosing may be undesirable because of the difficulties associated with storing and administering scheduled drugs within a school environment, the stigma associated with receiving medication during the school day, fragmented coverage with multiple short-acting doses, the potential for diversion of drug and the possible impact on adherence to the dosing regimen [100].

To extend the duration of action (i.e. symptomatic control) of stimulant medications, several long-acting formulations of MPH and AMF have been introduced that extend the pharmacokinetic and pharmacodynamic profile of the drugs (Table 1) [43, 61]. Most formulations depend on the slow, sustained release of the active ingredient in the stomach via the use of technologies such as wax matrix tablets, capsulated biphasic beads, or osmotically controlled release systems. Long-acting formulations mean that systemic exposure, and hence efficacy (symptom control), is maintained for longer periods, resulting in correspondingly improved convenience, confidentiality and compliance, more consistent coverage, and reduced abuse potential [43, 61, 75]. LDX is the first stimulant to use prodruk technology to modify the delivery profile. In its parent form, LDX is inactive and requires enzymatic cleavage in the blood to yield AMF. The combination of short- and long-acting formulations provides a range of treatment options lasting from approximately 4 h to more than 12 h. The demonstration that the efficacy of LDX in children is maintained for at least 13 h [97], suggests that this prodruk is the longest-acting stimulant formulation [25, 45]. However, since the drug needs to be absorbed and then cleaved in the bloodstream before it can be active, the onset of action may be somewhat delayed and may occur 1.5–2 h after ingestion [97]. In selecting an ADHD formulation, pharmacogenomics and non-genetic biomarkers may assist in the optimization and individualization of ADHD pharmacotherapy, although this is not yet possible [10, 19, 34, 44, 50, 89].
medication, stimulants may be contraindicated or the patient or caregivers may express a preference for non-stimulants. In such cases, a non-stimulant such as atomoxetine may be considered. Generally, the non-stimulants are considered less effective than the stimulants. Where stimulants are considered appropriate, the choice of short- or long-acting stimulant should be based on both clinical requirements and the preferences of an individual and their family [9].

Adherence to dosing regimen and persistence on therapy

Despite the carefully managed nature of the Multimodal Treatment Study of Children with ADHD (MTA), saliva assays for MPH revealed that approximately 25 % of 254 patients in the medication arms of the study were non-adherent on 50 % or more of repeated assays, and that barely half (54 %) were adherent at every assay point [67]. Furthermore, discrepancies were uncovered between parents' reports of adherence and the outcomes of the saliva assays [67]. These results indicate that there is considerable potential to improve pharmacotherapy outcomes by improving adherence. Several strands of evidence suggest that medication adherence may be improved by tailoring the selection of drug to an individual patient. Discrete choice experiments suggest that long-acting stimulants, with consistent therapeutic coverage throughout the day, are the preferred stimulant formulations of most patients [20, 42, 58, 64], and retrospective claims analyses suggest that long-acting stimulants are generally associated with enhanced adherence and persistence in patients of all ages compared with short-acting stimulants [20, 59, 80, 83]. In addition to drug regimens that patients find convenient, other strategies to improve adherence include improved communication between physicians, caregivers, and patients; clear instruction and encouragement; peer support groups; advice about reminders to take medication and incorporating medication into daily routines; and the use of positive reinforcement to improve attitudes to medication [66]. Addressing adverse events effectively may also contribute to promoting adherence.

Multimodal treatment

The importance of utilizing a multimodal treatment strategy that incorporates both medication and non-drug interventions is recognized by all ADHD clinical guidelines [1, 17, 66, 75, 91]. Indeed, as mentioned previously, non-drug interventions are the first-line treatment in school-aged children and adolescents with moderate ADHD and moderate impairment in many European countries [66, 91]. Behavioural therapy alone can produce improvements in ADHD compared with baseline [73]. In the MTA, for example, both medication and intensive behavioural therapy provided superior treatment outcomes to treatment in the community, even though the community treatment often included medication [92]. As the medication arm of the MTA was superior to both the behavioural and community treatment arms, these data provide further support for the notion that for medication treatments to achieve optimal effectiveness they need to be carefully titrated and monitored. The MTA also demonstrated that there were benefits in combining medication and behavioural therapy in certain non-core ADHD symptom domains (including aggression, internalizing symptoms, social skills, and parent–child relations), compared with either treatment approach alone [92]. Furthermore, non-adherence resulted in greater deleterious effects in the medication management group than in the combined treatment group [67]. The results from the MTA study confirmed those of earlier studies in children attending summer treatment programmes that demonstrated the reinforcing and synergistic outcomes of pharmacotherapy and behavioural therapy [18, 70, 71]. Together, these data illustrate the potential therapeutic advantages of combining intensive behavioural therapy with carefully crafted medication management [81].

Conclusions

Randomized and controlled clinical trials indicate that MPH and AMF offer robust medication options for the treatment of ADHD. In the drive to improve the treatment of ADHD for an individual, the nature of the stimulant, its formulation and optimization of the dosing regimen, with careful on-going monitoring of both positive and negative medication effects and adherence are all important considerations. Furthermore, concurrent non-drug treatments, including behavioural therapy, should all be considered as part of a multimodal treatment strategy. For those patients or caregivers who prefer not to take stimulants or for whom stimulants are contraindicated, non-stimulant drug options are available, though generally less effective.

Acknowledgments We thank Eric Southam of Oxford Pharma-Genesis Ltd for editorial assistance, collating of comments of authors, and editing the paper for submission. This editorial help was funded by Shire Development Inc., Wayne, PA, USA.

Conflict of interest Dr. Coghill has received speaker fees from Shire, Janssen Cilag, Medice, Lilly, UCB and Flynn Pharma; has served as a consultant or sat on advisory boards for Shire, Janssen Cilag, Shering-Plough, Pfizer, Lilly, Vifor and Flynn Pharma; has received research grants from Lilly, Janssen Cilag and Shire. Dr. Hechtman has served as a consultant or sat on advisory boards for Lilly, GlaxoSmith-Kline, Ortho Janssen, Purdue Pharma and Shire.
Reference

1. American Academy of Pediatrics (2011) ADHD: Clinical Practice Guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics 128:1007–1022
2. American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders, Fourth Edition, Text Revision (DSM-IV-TR). American Psychiatric Association, Washington DC
3. Antshel KM, Hargrave TM, Simoncescu M, Kaul P, Hendricks K, Faraone SV (2011) Advances in understanding and treating ADHD. BMC Med 9:72
4. Arnold EL (2000) Methylphenidate vs. amphetamine: comparative review. J Atten Disord 3:200–211
5. Arnold LE, Christopher J, Hueitis R, Smeltzer DJ (1978) Methylphenidate vs dextroamphetamine vs caffeine in minimal brain dysfunction: controlled comparison by placebos washout design with Bayes’ analysis. Arch Gen Psychiatry 35:463–473
6. Arinstein AF (2009) The emerging neurobiology of attention deficit hyperactivity disorder: the role of the prefrontal association cortex. J Pediatr 154:1–S43
7. Arinstein AF (2006) Fundamentals of attention-deficit/hyperactivity disorder: circuits and pathways. J Clin Psychiatry 67(Suppl 8):7–12
8. Assmann SF, Pocock SJ, Enos LE, Kasten LE (2000) Subgroup analysis and other (mis)uses of baseline data in clinical trials. Lancet 355:1064–1069
9. Banaschewski T, Coghill D, Santosh P, Zuddas A, Asherson P, Buitelaar J, Danckaerts M, Dompier M, Faraone SV, Rothenberger A, Sergeant J, Steinhausen HC, Sonuga-Barke EJ, Taylor E (2006) Long-acting medications for the hyperkinetic disorders. A systematic review and European treatment guideline. Eur Child Adolesc Psychiatry 15:476–495
10. Bellgrove MA, Barry E, Johnson KA, Cox M, Daibhis A, Daly M, Hawi Z, Lambert D, Fitzgerald M, McNicholas F, Robertson IH, Gill M, Kirley A (2008) Spatial attentional bias as a marker of genetic risk, symptom severity, and stimulant response in ADHD. Neuropsychopharmacology 33:2536–2545
11. Bonetti M, Gelber RD (2004) Patterns of treatment effects in subsets of patients in clinical trials. Biostatistics 5:465–481
12. Borcherding BG, Keyser CS, Cooper TB, Rapoport JL (1989) Differential effects of methylphenidate and dextroamphetamine on the motor activity level of hyperactive children. Neuropsychopharmacology 2:255–263
13. Brennan AR, Arinstein AF (2008) Neuronal mechanisms underlying attention deficit hyperactivity disorder: the influence of arousal on prefrontal cortical function. Ann N Y Acad Sci 1129:246–245
14. Brown GL, Hunt RD, Ebert MH, Bunney WE Jr, Kopin IJ (1979) Plasma levels of d-amphetamine in hyperactive children serial behavior and motor responses. Psychopharmacology 62:133–140
15. Burkins JA, Ciaverelli R, Frampton KK, Henschen G, McCarthy DP, Nardozzi LJ, Saldarini C, Scherzer A, Wadle C (2010) Clinical practice guideline for patients with attention deficit/hyperactivity disorder. Magellan Health Services Inc, MA, USA. https://www.magellanprovider.com/MHS/ML/convadinge/clinical_guidelines/clin_prac_guidelines/ADHD.pdf. Accessed 11 April 2012
16. Cai T, Tian L, Wong PH, Wei LJ (2011) Analysis of randomized comparative clinical trial data for personalized treatment selections. Biostatistics 12:270–282
17. Canadian Attention Deficit Disorder Resource Alliance (CADDRA) (2011) Canadian ADHD Practice (CAP) Guidelines, 3rd edn. Toronto, ON. http://www.caddra.ca/cms/4/pdfs/caddraGuidelines2011.pdf. Accessed 11 April 2012
18. Carlson CL, Pelham WE Jr, Milich R, Dixon J (1992) Single and combined effects of methylphenidate and behavior therapy on the classroom performance of children with attention-deficit hyperactivity disorder. J Abnorm Child Psychol 20:213–232
19. Castellanos FX, Elia J, Kruesi MJ, Marsi WL, Gulotta CS, Potter WX, Ritchie GF, Hamburger SD, Rapoport JL (1996) Cerebrospinal fluid homovanillic acid predicts behavioral response to stimulants in 45 boys with attention deficit/hyperactivity disorder. Neuropsychopharmacology 14:125–137
20. Christensen L, Sasse R, Hodgkins P, Harley C, Tetal T (2010) Pharmacological treatment patterns among patients with attention-deficit/hyperactivity disorder: retrospective claims-based analysis of a managed care population. Curr Med Res Opin 26:977–989
21. Cohen J (1992) A power primer. Psychol Bull 112:155–159
22. Curatolo P, D’Agati E, Mavero R (2010) The neurobiological basis of ADHD. Ital J Pediatr 36:79
23. Dahbreh IJ, Terasawa T, Castaldi PI, Trikalinos TA (2011) Systematic review: anti-epidermal growth factor receptor treatment effect modification by KRAS mutations in advanced colorectal cancer. Ann Intern Med 154:37–49
24. Deutsche Gesellschaft für Kinder- und Jugendpsychiatrie und Psychotherapie: Leitlinien zur Diagnostik und Therapie von psychischen Störungen im Säuglings-Kind (2007) Hyperkinetische Störungen (F90). http://www.awmf.org/uploads/tx_szleitlinien/028-019_S1_HyperkinetischeStoerungenADHS_01.pdf. Accessed 5 April 2012
25. Dew RE, Kollins SH (2010) Lisdexamfetamine dimesylate: a new option in stimulant treatment for ADHD. Expert Opin Pharmacother 11:2907–2913
26. Diamond A (2005) Attention-deficit-hyperactivity disorder (attention-deficit/hyperactivity disorder without hyperactivity): a neurobiologically and behaviorally distinct disorder from attention-deficit/hyperactivity disorder (with hyperactivity). Dev Psychopathol 17:807–825
27. Dopheide JA (2009) The role of pharmacotherapy and managed care pharmacy interventions in the treatment of ADHD. Am J Manag Care 15:S141–S150
28. Early Breast Cancer Trialists’ Collaborative Group (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 365:1687–1717
29. Early Breast Cancer Trialists’ Collaborative Group (1998) Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet 351:1451–1467
30. Easton N, Steward C, Marshall F, Fone K, Marsden C (2007) Effects of amphetamine isomers, methylphenidate and atomoxetine on synaptosomal and synaptic vesicle accumulation and release of dopamine and noradrenaline in vitro in the rat brain. Neuropharmacology 52:405–414
31. Efron D, Jarman F, Barker M (1997) Methylphenidate versus dexamphetamine in children with attention deficit hyperactivity disorder: a double-blind, crossover trial. Pediatrics 100:667–672
32. Efron D, Jarman F, Barker M (1997) Side effects of methylphenidate and dexamphetamine in children with attention deficit

Open Access This article is distributed under the terms of the Creative Commons Attribution License which permits any use, distribution, and reproduction in any medium, provided the original author(s) and the source are credited.
33. Elia J (2005) Attention deficit/hyperactivity disorder: pharmacotherapy. Psychiatry (Edgmont) 2:27–35
34. Elia J, Borcherding BG, Potter WZ, Meford IN, Rapoport JL, Keysor CS (1990) Stimulant drug treatment of hyperactivity: biochemical correlates. Clin Pharmacol Ther 48:57–66
35. Elia J, Borcherding BG, Rapoport JL, Keysor CS (1991) Methylphenidate and dextroamphetamine treatments of hyperactivity: are there true nonresponders? Psychiatry Res 36:141–155
36. Elia J, Welsh PA, Gullotta CS, Rapoport JL (1993) Classroom academic performance: improvement with both methylphenidate and dextroamphetamine in ADHD boys. J Child Psychol Psychiatry 34:785–804
37. Faraone SV (2012) Understanding the effect size of lisdexamfetamine dimesylate for treating ADHD in children and adults. J Atten Disord 16:128–137
38. Faraone SV (2009) Using meta-analysis to compare the efficacy of medications for attention-deficit/hyperactivity disorder in youths. P T 34:678–694
39. Faraone SV, Buitelaar J (2010) Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. Eur Child Adolesc Psychiatry 19:353–364
40. Faraone SV, Glatt SJ (2009) A comparison of the efficacy of medications for adult attention-deficit/hyperactivity disorder using meta-analysis of effect sizes. J Clin Psychiatry 71:754–763
41. Faraone SV, Mick E (2010) Molecular genetics of attention deficit hyperactivity disorder. Psychiatr Clin N Am 33:159–180
42. Fegert JM, Slawik L, Wermelskirchen D, Nubling M, Muhlbacher A (2011) Assessment of parents’ preferences for the treatment of school-age children with ADHD: a discrete choice experiment. Expert Rev Pharmacoecon Outcomes Res 11:245–252
43. Findling RL (2002) Evolution of the treatment of attention-deficit/hyperactivity disorder in children: a review. Clin Ther 30:942–957
44. Froehlich TE, McGough JJ, Stein MA (2010) Progress and promise of attention-deficit/hyperactivity disorder pharmacogenetics. CNS Drugs 24:99–117
45. Goodman DW (2010) Lisdexamfetamine dimesylate (vyvanse), a prodrug stimulant for attention-deficit/hyperactivity disorder. P T 35:273–287
46. Graham J, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, Dittmann RW, Dogfner M, Hamilton R, Hollis C, Holtmann M, Hulpke-Wette M, Lecendreux M, Rosenhall E, Rohrberger A, Santosh P, Sergeant J, Simonoff E, Sonuga-Barke E, Wong IC, Zuddas A, Steinhausen HC, Taylor E (2011) European guidelines on managing adverse effects of medication for ADHD. Eur Child Adolesc Psychiatry 20:17–37
47. Graham J, Coghill D (2008) Adverse effects of pharmacotherapies for attention-deficit hyperactivity disorder: methodology, prevention and management. CNS Drugs 22:213–237
48. Heal DJ, Smith SL, Findling RL (2012) ADHD: current and future therapeutics. Curr Top Behav Neurosci 10:361–390
49. Heal DJ, Smith SL, Kulkarni RS, Rowley HL (2008) New perspectives from microdialysis studies in freely-moving, spontaneously hypertensive rats on the pharmacology of drugs for the treatment of ADHD. Pharmacol Biochem Behav 90:184–197
50. Hersens DF, Cooper NJ, Kohn M, Clarke S, Gordon E (2005) Predicting stimulant medication response in ADHD: evidence from an integrated profile of neuropsychological, psychophysiological and clinical factors. J Integr Neurosci 4:107–121
51. Hungund BL, Perel JM, Hurwic MJ, Sverd J, Winsberg BG (1979) Pharmacokinetics of methylphenidate in hyperkinetic children. Br J Clin Pharmacol 8:571–576
52. Jones SR, Gainedtino RR, Wightman RM, Caron MG (1998) Mechanisms of amphetamine action revealed in mice lacking the dopamine transporter. J Neurosci 18:1979–1986
53. Kahlig KM, Bind A, Khoshbouei H, Blakely RD, McMahon DG, Javitch J, Galil A (2005) Amphetamine induces dopamine efflux through a dopamine transporter channel. Proc Natl Acad Sci USA 102:3495–3500
54. Karapetis CS, Khambatta-Ford S, Jonker DJ, O’Callaghan CJ, Tu D, Tebbutt NC, Simes RJ, Chalchal H, Shapiro JD, Robitaille S, Price TJ, Shepherd L, Au HJ, Langer C, Moore MJ, Zalcberg JR (2008) K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 359:1757–1765
55. Kuczynski R, Segal DS (1997) Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: comparison with amphetamine. J Neurochem 68:2032–2037
56. Lagakos SW (2006) The challenge of subgroup analyses–reporting without distorting. N Engl J Med 354:1667–1669
57. Läkemedelsverket (2009) Läkemedelsbehandling av ADHD—Ny rekommendation. http://www.lakemedelsverket.se/upload/halsoc-sjukvard/behandlingsrekommerndationen/ADHD-rek_webb.pdf. Accessed 5 April 2012
58. Lloyd A, Hodgkins P, Dewilde S, Sasané R, Falcner S, SB E (2011) Methylphenidate delivery mechanisms for the treatment of children with attention deficit hyperactivity disorder: Heterogeneity in parent preferences. Int J Technol Assess Health Care 27:215–223
59. Marcus SC, Wan GJ, Kemner JE, Olfsen M (2005) Continuity of methylphenidate treatment for attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med 159:572–578
60. Markowitz JS, DeVane CL, Pestreich IJ, Patrick KS, Muniz R (2006) A comprehensive in vitro screening of d-, l- and dl-threo-methylphenidate: an exploratory study. J Child Adolesc Psychopharmacol 16:687–698
61. May DE, Kratochvil CJ (2010) Attention-deficit hyperactivity disorder: recent advances in paediatric pharmacotherapy. Drugs 70:15–40
62. McDonagh M, Peterson K, Dana T, Thakurta S (2007) Drug Class Review on Pharmacologic Treatments for ADHD. http://www.ncbi.nlm.nih.gov/books/ bookres.fcgi/adhd/pfd/adhd.pdf. Accessed 27 September 2011. Oregon Health and Science University, Portland, Oregon
63. Ministerio de Sanidad PSeI (2010) Guı́a de Práctica Clı́nica sobre el trastorno por de ﬂicit de atención con hiperactividad (TDAH) en niños y adolescentes. http://www.gencat.cat/salut/salutgencat/docs/units/aatrm/pdf/gpc_tdah_hiperactividad_aiaqs2010_compl.pdf. Accessed 5 April 2012
64. Muhlbacher AC, Rudolph I, Lincke HJ, Nubling M (2009) Preferences for treatment of attention-deficit/hyperactivity disorder (ADHD): a discrete choice experiment. BMC Health Serv Res 9:149
65. National Health Service (2009) National Institute for Health and Clinical Excellence Guideline Number 72. London, UK. http://www.nice.org.uk/nicemedia/live/12061/42060/42060.depdf. Accessed 11 April 2012
66. National Health Service (2010) Prescription cost analysis, England–2010. http://www.ic.nhs.uk/statistics-and-data-collections/primary-care/prescriptions/prescription-cost-analysis-england-2010. Accessed 1 June 2011
67. Pappadopulos E, Jensen PS, Chait AR, Arnold LE, Swanson JM, Greenhill LL, Hechtman L, Chuang S, Wells KC, Pelham W, Cooper T, Elliott G, Newcorn JH (2009) Medication adherence in the MTA: saliva methylphenidate samples versus parent report and mediating effect of concomitant behavioral treatment. J Am Acad Child Adolesc Psychiatry 48:501–510
68. Pelham WE, Aronoff HR, Midlam JK, Shapiro CJ, Gnagy EM, Chronis AM, Onyango AN, Forehand G, Nguyen A, Waxmonsky J (1999) A comparison of ritalin and adderal: efficacy and time-course in children with attention-deficit/hyperactivity disorder. Pediatrics 103:e43

69. Pelham WE, Gnagy EM, Chronis AM, Burrows-MacLean L, Fabiano GA, Onyango AN, Meichenbaum DL, Williams A, Aronoff HR, Steiner RL (1999) A comparison of morning-only and morning/late afternoon Adderal to morning-only, twice-daily, and three times-daily methylphenidate in children with attention-deficit/hyperactivity disorder. Pediatrics 104:1300–1311

70. Pelham WE, Gnagy EM, Greiner AR, Hoza B, Hinshaw SP, Swanson JM, Simpson S, Shapiro C, Balstein O, Baron-Myk C, McBurnett K (2000) Behavioral versus behavioral and pharmacological treatment in ADHD children attending a summer treatment program. J Abnorm Child Psychol 28:507–525

71. Pelham WE Jr, Carlson C, Sams SE, Vallano G, Dixon MJ, Hoza B (1993) Separate and combined effects of methylphenidate and behavior modification on boys with attention deficit-hyperactivity disorder in the classroom. J Consult Clin Psychol 61:506–515

72. Pelham WE Jr, Greenslade KE, Vodde-Hamilton M, Murphy DA, Greenstein JJ, Gnagy EM, Guthrie JJ, Hoover MD, Dahl RE (1990) Relative efficacy of long-acting stimulants on children with attention deficit-hyperactivity disorder: a comparison of standard methylphenidate, sustained-release methylphenidate, sustained-release dextroamphetamine, and pemoline. Pediatrics 86:226–237

73. Pelham WE Jr, Wheeler T, Chronis A (1998) Empirically supported psychosocial treatments for attention deficit hyperactivity disorder. J Clin Child Psychol 27:190–205

74. Peto R (1990) Misleading subgroup analyses in GISSI. Am J Cardiol 66:771–772

75. Pliszka S (2007) Practice parameter for the assessment and metaregression analysis. Am J Psychiatry 164:942–948

76. Pliszka SR, Browne RG, Olvera RL, Wynne SK (2000) A double-blind, placebo-controlled study of Adderall and methylphenidate in the treatment of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 39:619–626

77. Pliszka SR, Crismon ML, Hughes CW, Corners CK, Emslie GJ, Jensen PS, McCracken JT, Swanson JM, Lopez M (2006) The Texas Children’s Medication Algorithm Project: revision of the algorithm for pharmacotherapy of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 45:642–657

78. Pocock SJ, Assmann SE, Enos LE, Kasten LE (2002) Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems. Stat Med 21:2917–2930

79. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA (2007) The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry 164:942–948

80. Ramos-Quiroga JA, Bosch R, Castells X, Valero S, Nogueira M, Sanchez RJ, Crismon ML, Barner JC, Bettinger T, Wilson JP (2005) Assessment of adherence measures with different stimulants among children and adolescents. Pharmacotherapy 25:909–917

81. Perez-Cerda F (2002) Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems. Stat Med 21:2917–2930

82. Robertson SD, Matthes HJ, Galli A (2009) A closer look at amphetamine-induced reverse transport and trafficking of the dopamine and norepinephrine transporters. Mol Neurobiol 39:73–80

83. Sanchez RJ, Crismon ML, Barner JC, Bettinger T, Wilson JP (2005) Assessment of adherence measures with different stimulants among children and adolescents. Pharmacotherapy 25:909–917

84. Scottish Intercollegiate Guidelines Network (2009) Management of attention deficit and hyperkinetic disorders in children and young people: a national clinical guideline. http://www.sign.ac.uk/pdf/sign112.pdf. Accessed 5 April 2012

85. Seixas M, Weiss M, Muller U (2012) Systematic review of national and international guidelines on attention-deficit hyperactivity disorder. J Psychopharmacol 26:753–765

86. Sharp WS, Walter JM, Marsh WL, Ritchie GF, Hamburger SD, Castellanos FX (1999) ADHD in girls: clinical comparability of a research sample. J Am Acad Child Adolesc Psychiatry 38:40–47

87. Solomon SD, Rice MM, Jablonski JA, Jose P, Domanski M, Sabatine M, Gersh BJ, Roulreau J, Pfeffer MA, Braunwald E (2006) Renal function and effectiveness of angiotensin-converting enzyme inhibitor therapy in patients with chronic stable coronary disease in the Prevention of Events with ACE inhibition (PEACE) trial. Circulation 114:26–31

88. Steele M, Jensen PS, Quinn DM (2006) Remission versus response as the goal of therapy in ADHD: a new standard for the field? Clin Ther 28:1892–1908

89. Stein MA, McGough JJ (2008) The pharmacogenomic era: promise for personalizing attention deficit hyperactivity disorder therapy. Child Adolesc Psychiatr Clin N Am 17:475–490, xi–xii

90. Sulzer D, Sonders MS, Poulsen NV, Galli A (2005) Mechanisms of neurotransmitter release by amphetamines: a review. Prog Neurobiol 75:406–433

91. Taylor E, Dopfer M, Sergeant J, Asherson P, Banaschewski T, Pelham WE, Aronoff HR, Steiner RL (1999) A comparison of morning-only and morning/late afternoon Adderall to morning-only, twice-daily, and pemoline. Pediatrics 86:226–237

92. Taylor E, Dopfer M, Sergeant J, Asherson P, Banaschewski T, Pelham WE, Aronoff HR, Steiner RL (1999) A comparison of morning-only and morning/late afternoon Adderall to morning-only, twice-daily, and pemoline. Pediatrics 86:226–237

93. The Royal Australasian College of Physicians (2009) Australian guidelines on attention deficit hyperactivity disorder (ADHD). http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synops es/adhd/NHMRC-draft-ADHD-guidelines.pdf. Accessed 01 June 2011

94. Tian L, Cai T, Wei LJ (2009) Identifying subjects who benefit from additional information for better prediction of the outcome variables. Biometrics 65:894–902

95. Volkow ND, Fowlser JS, Wang G, Ding Y, Gatley SJ (2002) Mechanism of action of methylphenidate: insights from PET imaging studies. J Atten Disord 6(Suppl 1):S31–S43

96. Volkow ND, Wang GJ, Fowlser JS, Gatley SJ, Logan J, Ding YS, Hitzemann R, Pappas N (1998) Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. Am J Psychiatry 155:1325–1331

97. Wigal SB, Kollins SH, Childress AC, Squires L (2009) A 13-hour laboratory school study of lisdexamfetamine dimesylate in school-aged children with attention-deficit/hyperactivity disorder. Child Adolesc Psychiatr Ment Health 3:17

98. Wilson HK, Coburn J, Merkel RL, Moore M, Coghill D, Winsberg BG, Press M, Bialer I, Kupietz S (1974) Dextroamphetamine and methylphenidate in the treatment of hyperactive-aggressive children. Pediatrics 53:236–241
100. Wolraich ML, Doffing MA (2004) Pharmacokinetic considerations in the treatment of attention-deficit hyperactivity disorder with methylphenidate. CNS Drugs 18:243–250
101. World Health Organization Collaborating Centre for Drug Statistics and Methodology (2011) ATC/DDD Index 2011. http://www.whocc.no/atc_ddd_index/
102. Zhao L, Cai T, Tian L, Uno H, Solomon SD, Wei LJ (2010) Stratifying subjects for treatment selection with censored event time data from a comparative study. Harvard University Biostatistics Working Paper Series 2010:Working Paper 122