CNS Drugs (2014) 28:1005–1033
DOI 10.1007/s40263-014-0175-1

REVIEW ARTICLE

A Review of OROS Methylphenidate (Concerta®) in the Treatment of Attention-Deficit/Hyperactivity Disorder

Martin A. Katzman · Tia Sternat

Published online: 14 August 2014

Abstract Attention-deficit/hyperactivity disorder (ADHD) is a common neurobehavioural disorder with onset during childhood. It affects a child's development, both at home and at school, and impacts on social, emotional and cognitive functioning, in both the home and the school environment. Untreated ADHD is very often associated with poor academic achievement, low occupational status, increased risk of substance abuse and delinquency. Current practice guidelines recommend a multimodal approach in the treatment of ADHD, which includes educational, behavioural and mental health interventions, and pharmacological management. Stimulant medications, including methylphenidate (MPH) and amphetamine products, are recommended as first-line pharmacotherapy in the treatment of ADHD. The choice of stimulant is influenced by several factors; the most influential factor is the duration of action. Long-acting medication provides benefits long after school and work. It also increases the likelihood of once-daily dosing, thereby eliminating the need for mid-day dosing, making the treatment more private, avoiding stigma and improving adherence to medication. MPH is the most widely used psychotropic medication in child psychiatry. It was first developed for use in children as an oral, immediate-release formulation and more recently as various extended-release formulations. These latter formulations include the 12 h preparation Concerta® (osmotic-release oral system [OROS] MPH), which utilizes an osmotic pump system, designed to overcome the difficulties of multiple daily dosing. Since it received approval from the US Food and Drug Administration in August 2000, OROS MPH has been quickly and widely accepted as one of the preferred treatments for ADHD because of its once-daily dosing. This paper reviews the data in support of long-acting OROS MPH in children, adolescents and adults, both in ADHD and in association with its comorbidities.

M. A. Katzman (✉) · T. Sternat
START Clinic for Mood and Anxiety Disorders,
32 Park Road, Toronto,
ON M4W 2N4, Canada
e-mail: mkatzman@startclinic.ca

M. A. Katzman
Northern Ontario School of Medicine, Thunder Bay,
ON, Canada

M. A. Katzman
Department of Psychology, Lakehead University,
Thunder Bay, ON, Canada

M. A. Katzman
University of Toronto, Toronto,
ON, Canada

M. A. Katzman · T. Sternat
Adler Graduate Professional School, Toronto,
ON, Canada

T. Sternat
Janssen Inc., Toronto, ON, Canada

Key Points

Treatment with osmotic-release oral system (OROS) methylphenidate (MPH), as with all extended-release formulations of MPH, offers benefits not only to children and adolescents with ADHD but also to adults with ADHD.

Treatment with OROS MPH, as with all extended-release formulations of MPH, offers improvements in core ADHD symptoms, in performance (of academic, behavioural and cognitive tasks) and in different domains of attention and executive functioning.

The greatest benefit of OROS MPH lies in its ability to offer symptomatic control not only during the traditional school day (or in adults during the work day) but also in the evening.

1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the more common neurobehavioural disorders of childhood. The lifetime prevalence is reported to be 6–9 % in children, with 70 % persistence of ADHD into adolescence and 50–65 % persistence into adulthood [1–3].

The global prevalence of ADHD is estimated to be 5.9–7.1 % among children and adolescents [4] and 3.4–4.4 % among adults [2, 5]. ADHD affects a child's development, both at home and at school, and impacts on social, emotional and cognitive functioning in both the home and the school environment [6]. Untreated ADHD leads to poor academic achievement, low occupational status, increased risk of substance abuse and delinquency.

Current practice guidelines call for appropriate assessment and treatment of ADHD in children to ensure that sufferers experience full and harmonious development [6–15]. A multimodal approach is recommended, including educational, behavioural and mental health interventions, and pharmacological management. Although educational, behavioural and mental health interventions play important roles in effective management of ADHD, pharmacological management is the most widely researched intervention. Current guidelines recommend stimulant medications, including methylphenidate (MPH) and amphetamine products, as well as the selective norepinephrine reuptake inhibitor atomoxetine, as first-line pharmacotherapy for the treatment of ADHD. Throughout Europe, the use of all medicines containing MPH has been approved for the treatment of ADHD in children aged 6 years and older, and in adolescents [16, 17]. MPH and lisdexamphetamine (LDX) are approved in Europe for adults with ADHD whose symptoms persist from adolescence into adulthood [18, 19], while MPH pellets have been approved for the treatment of newly diagnosed adults with ADHD in Germany [20]. In Canada and the USA, MPH products, atomoxetine and LDX are approved for the treatment of ADHD in children, adolescents and adults [21–28].

The choice of stimulant is influenced by several factors [9]. Perhaps the most influential factor is the duration of action. Children, adolescents and adults benefit from a long-acting medication, which provides a benefit after school for extracurricular activities and homework, improves social and occupational functioning throughout the day and increases the ability to meet family responsibilities in the evening. Moreover, long-acting medications allow for once-daily dosing, which eliminates the need for mid-day dosing at school, making the treatment more private, avoiding stigma at school and thereby improving adherence to medication [10, 29–31].

MPH is the most widely used psychotropic medication in child psychiatry [32]. It was first developed for use in children as an oral, immediate-release formulation (IR MPH), and this formulation for all intents and purposes has remained unchanged since its introduction in 1957. MPH is rapidly and almost completely absorbed, and attains its maximum blood concentration (C_{max}) within 1–3 h [33]. The rapid uptake of IR MPH into the central nervous system is attributed to its rapid distribution, low protein binding and high lipid solubility.

IR MPH has been shown to markedly and rapidly reduce the overt and less overt clinical manifestations of ADHD [10], showing improved quality of social interactions and decreased aggressiveness. However, IR MPH provides relief from ADHD symptoms for approximately 4 h only, therefore necessitating multiple daily dosing to maintain a benefit throughout the day [33]. Because of the shorter period of efficacy, and therefore increased difficulties with adherence to the precise 4 h dosing, the patient on IR MPH spends a lower percentage of time per day within the therapeutic range of MPH [34, 35].

The extended-release preparations of MPH (ER MPH), such as the 8 h preparations Metadate® CD and Ritalin® LA, which utilize a microbead technology, and the most recent 12 h preparation Concerta® [osmotic-release oral system (OROS) MPH], which utilizes an osmotic pump system, have been designed to overcome the difficulties of multiple daily dosing. Since it received approval from the US Food and Drug Administration (FDA) in August 2000, OROS MPH has been quickly and widely accepted because of its once-daily dosing [36].

2 The Neurobiology of Stimulants

As a class, psychostimulants exert their effects by increasing the availability of synaptic dopamine [37, 38]. MPH is believed to bind the dopamine transporter in the presynaptic cell membrane, thereby blocking the reuptake of dopamine and causing an increase in extracellular dopamine levels, while amphetamine products are hypothesized to increase synaptic dopamine by causing the release of newly synthesized cytosolic dopamine from the nerve terminal. Indirectly, there may be reuptake of both dopamine and norepinephrine into the presynaptic neuron, facilitating neurotransmitter release through reverse transport [39, 40]. A significant amount of research has been done on the pharmacogenomics of MPH, including studies on the dopamine transporter gene *SLC6A3/DAT1*, the dopamine D4 receptor gene *DRD4*, the α_{2A}-adrenergic receptor gene *ADRA2A* and the catechol-*O*-methyl-transferase gene *COMT*. This topic has been extensively reviewed by Kieling et al. [41]. Because we cannot, in an a priori manner, know which stimulant will be a better choice for a specific patient, it behoves the clinician to try both classes of stimulants before deciding on the definitive course of action for the specific patient. This approach has been supported by a number of algorithms [8, 42, 43].

While both options (amphetamines and MPHs) are more than appropriate choices, this review summarizes and presents the latest data on the use of OROS MPH in the treatment of ADHD, with a focus on comorbidities associated with ADHD, with some hypothesized possible differences between patients who respond to MPHs and those who respond to amphetamines. The studies discussed in this review were identified using the following search terms in PubMed: 'ADHD', 'adolescent', 'adult', 'amphetamine', 'atomoxetine', 'children', 'methylphenidate' and 'OROS methylphenidate'.

3 Review of Clinical Trials for Use of MPH in Children (6–12 Years of Age): Focus on OROS MPH

Pelham et al. [44] tested the efficacy and duration of action, in both the natural and laboratory settings, of three treatment conditions (OROS MPH given once daily [qd] in the morning, IR MPH given three times daily [tid] and placebo) in a within-subject, double-blind, crossover comparison. The study enrolled 68 children (aged 6–12 years), and each child received each medication condition for a 7-day period. The medications were given at three dosing levels, where the dose of OROS MPH was designed to last 12 h and equivalent to tid dosing of IR MPH. The comparison dosing levels were IR MPH 5 mg tid/OROS MPH 18 mg qd; IR MPH 10 mg tid/OROS MPH 36 mg qd; and IR MPH 15 mg tid/OROS MPH 54 mg qd. At enrolment, all children were receiving MPH, and each child's dose level for the study was based on that child's MPH dosing before the study. Overall, in comparison with placebo, both IR MPH and OROS MPH conferred significant improvement in all dependent measures taken in the natural setting ($p < 0.001$). These included teacher ratings of inattention/overactivity and oppositional/defiant behaviour, as well as parent ratings of inattention/overactivity and oppositional/defiant behaviour. Two differences between OROS MPH and IR MPH were observed: the parent ratings of inattention/overactivity and the Abbreviated Conners Scale scores. For both measures, the ratings in the OROS MPH condition were superior to those in the IR MPH condition ($p < 0.05$). At the end of the study, when parents were asked to choose which of the treatment weeks they preferred, 47 % chose the OROS MPH week, 31 % chose the tid IR MPH week, 15 % chose their previous MPH treatment and the remainder chose placebo or had no preference. In the laboratory setting, OROS MPH was superior to placebo and not significantly different from tid IR MPH, even at 12 h after dosing. This study was the first to demonstrate that OROS MPH had significant effects through 12 h after dosing in both the natural and laboratory settings, indicating that the span of action of OROS MPH is comparable to tid IR MPH.

The safety and efficacy of OROS MPH over 28 days was determined in a multicentre, randomized, double-blind, placebo-controlled clinical trial enrolling 282 children (aged 6–12 years) with ADHD [45]. Subjects were randomized to placebo ($n = 90$), IR MPH tid (dosed every 4 h; $n = 97$), or OROS MPH qd ($n = 95$). Subjects in the OROS MPH and IR MPH groups demonstrated significantly greater reductions in core ADHD symptoms, measured as mean teacher and parent IOWA Conners Scale ratings, than did subjects on placebo, both at the end of week 1 and at the end of the study. There were no differences between the OROS MPH group and the IR MPH group. Treatment discontinuations were recorded for 48 % of subjects in the placebo arm, compared with 16 and 14 % of those in the OROS MPH and IR MPH arms, respectively. At least one adverse event was reported by 42.3 % of patients in the OROS MPH group and by 46.2 % of patients in the IR MPH group. The majority of events were mild in nature, and the most common treatment-related adverse events were headache (occurring in 14.4, 5.8 and 10.2 % of patients in the OROS MPH, IR MPH and placebo groups, respectively), and abdominal pain (occurring in 6.7, 5.8 and 1.0 % of patients in the OROS MPH, IR MPH and placebo groups, respectively). These findings showed that OROS MPH and IR MPH were superior to placebo for the treatment of core ADHD symptoms, and that OROS MPH and IR MPH were not different from each

other. Similar observations were reported by Lee et al. [46] in an open-label, multicentre, 4-week trial among 119 children (aged 6–13 years) with ADHD, who received an average daily dose of OROS MPH 0.87 mg/kg. By the end of the study, the mean teacher and parent IOWA Conners Scale ratings had decreased significantly and peer interaction scores had improved significantly, compared with baseline. In addition, the study investigators rated overall symptom reduction as 'very much improved' for 14 % of the children, 'much improved' for 54 % and 'minimally improved' for 24 %. Forty-five children experienced at least one mild or moderate adverse event, with the common complaints being anorexia (26.1 %), insomnia (21.7 %), headache (14.5 %), vomiting (7.2 %) and abdominal pain (5.8 %), tics (5.8 %), fatigue (4.3 %), nausea (4.3 %), dizziness (4.3 %), rash (3.9 %), dyspepsia (1.4 %) and nervousness (1.4 %). A larger, 6-week, multicentre, open-label study in 1,447 children with ADHD also reported significant improvements in parent IOWA Conners Scale scores, as well as significant symptom reduction [47]. Adverse events were reported by 35.3 % of patients, with the majority of the events being mild in nature. The most common adverse events were anorexia (47.9 %), insomnia (12.6 %), headache (12.4 %) and stomach ache (12.1 %).

These findings are further supported by a study conducted by Song et al. [48] in children and adolescents (patients aged 6–18 years) who achieved clinical response with OROS MPH. Study investigators reported that over 12 weeks, 77 of 116 patients (66.4 %) achieved the criteria for response, defined as a Korean ADHD Rating Scale (K-ARS) score of <18 and a Clinical Global Impression—Improvement Scale (CGI-I) score of 6 or 7. The average daily dose of OROS MPH required for response was 30.05 ± 12.52 mg/day (0.90 ± 0.31 mg/kg/day) at the end of the study. The most common adverse events were anorexia (31.0 %), insomnia (13.1 %), headache (8.9 %), abdominal pain (6.0 %) and dizziness (4.5 %).

The long-term efficacy and safety of OROS MPH was assessed over 24 months in 407 children (aged 6–13 years) with ADHD in an open-label, multicentre study [49]. Subjects initially received a daily dose of OROS MPH 18–54 mg with upward or downward dose adjustment in 18 mg increments, based on clinical response and adverse events. Throughout the study period, multiple measures of ADHD symptoms, vital signs, weight, height and laboratory results were measured. After the first 12 months, 71 % of subjects (289/407) completed treatment, and OROS MPH was found to be well tolerated, with subjects reporting adverse events similar to those previously reported for IR MPH [50]. The effectiveness of OROS MPH was stable over this time, as shown by stable IOWA Conners Scale ratings and sustained improvements in peer interaction and Global Assessment Scale scores. This was the first study to report the efficacy and tolerability of OROS MPH over 12 months in children with ADHD.

At the end of 24 months, a total of 229 subjects (57 % of the total 407 who enrolled; 79 % of those enrolled at 12 months) completed the study [49]. The mean daily increase in the OROS MPH dose over the 24 months was 26 %, from 35.2 mg at baseline to 44.2 mg at the end of the study, with the majority of the dose increases occurring in the first year of the study. Treatment with OROS MPH was generally well tolerated, with only 7.6 % of the subjects (31/407) discontinuing treatment because of adverse events. In addition, minimal effects on growth in height and weight were observed, and no clinically significant effects on laboratory test parameters or vital signs were observed. Overall efficacy, measured as both parent/caregiver global assessment values, ranged from 87 % at month 3 to 95 % at the end of the study. Efficacy measured by investigator assessment values for the second year of treatment ranged from 91 to 95 %. Overall, 85 % of parent/caregiver measures and 92 % of investigator-rated treatment measures were rated as 'good' or 'excellent', and 86 % of parents/caregivers were 'pleased', 'very pleased' or 'extremely pleased' with OROS MPH, corresponding to a very high level of satisfaction. These findings demonstrated continued efficacy and tolerability of OROS MPH for up to 2 years in children with ADHD.

In recent years, the beneficial effects of OROS MPH on functioning, severity of disease, quality of life (QoL), academic performance, cognition and social behaviour in children with ADHD have been assessed, most recently by Gerwe et al. [51] and Wigal et al. [52]. Gerwe et al. [51] assessed the tolerability of OROS MPH, as well as its efficacy in improving social functioning in four important areas of life (school, recreation, family life and peer interaction). The severity of disease and QoL were also assessed in this study in children and adolescents (aged 6–14 years) with ADHD. This 8-week, prospective, open-label, single-arm, noninterventional trial enrolled 306 subjects who initiated therapy with OROS MPH, or who transitioned from IR MPH to OROS MPH. Significant improvements in all four important areas of life were observed ($p < 0.0001$), regardless of whether the subject was initiating treatment with OROS MPH or switching to OROS MPH. Demonstrated improvement in the school situation was noted in 56.2 % of subjects, in the recreational area in 50.7 % of subjects, in the family area in 58.8 % of subjects and in peer interactions in 47.4 % of subjects. In addition, the severity of disease was significantly improved by the end of the study ($p < 0.0001$), with 81.0 % of all subjects experiencing an improvement in the severity of disease and 73.9 % of parents reporting an improvement in QoL for the family. A total of 319 adverse events were reported by 52.3 % of patients, with the most

common being insomnia (10.8 %), anorexia (7.8 %), ineffectiveness of medication (7.8 %) and headache (5.6 %).

In a subsequent double-blind, randomized, placebo-controlled, crossover, laboratory school study enrolling 78 children (aged 9–12 years) with ADHD who responded to OROS MPH, subjects received blinded treatment (OROS MPH or placebo, then vice versa) on each of two laboratory school days, separated by 1 week [52]. Compared with the placebo day, on the OROS MPH day, subjects demonstrated significant improvements in Permanent Product Measure of Performance scores and Swanson, Kotkin, Agler, M-Flynn and Pelham Rating Scale (SKAMP) scores, as well as in measures of response time and working memory. Half of the patients (50 %) reported at least one treatment-emergent adverse event. Most were mild to moderate in nature, and the most common were decreased appetite (25.6 %), abdominal pain (16.7 %), headache (16.7 %) and irritability (14.4 %). These findings showed that when OROS MPH is dosed to reduce core symptoms of ADHD to within the normal range, it also improves performance on a variety of academic tasks in school-aged children. Similar results have been published in recent years regarding the efficacy of OROS MPH in different domains of attention and executive functioning, and in academic, behavioural and cognitive tasks, in children with ADHD [53, 54].

Although children with ADHD benefit from treatment resulting in symptom control during the school day, evidence from the literature points to the equal importance of controlling symptoms after school when concentration and performance contribute to the development of a child's personal and social skills [55]. In a pan-European survey of parents of children and adolescents (aged 6–18 years) with and without ADHD, parents reported that children with ADHD treated with 12 h stimulant medication experienced fewer challenges during the early afternoon and late afternoon/early evening than children treated with 6 h to 8 h stimulant medication [56]. The survey also revealed that, although the majority (68 %) of parents were satisfied with their child's current treatment, 35–40 % specifically reported that their child's ADHD symptoms were not adequately controlled during the afternoon and evening.

Two laboratory school studies by Pelham et al. [44] and Swanson et al. [32] demonstrated that in comparison with placebo, OROS MPH treatment resulted in improvements in attention and behaviour that were sustained for 12 h, and therefore covered the school day as well as homework times and other after-school activities. These findings were supported by Favreau et al. [57], who further demonstrated the efficacy of OROS MPH in the late afternoon and homework time. Furthermore, as per the parents' preference, OROS MPH was finally requested in more than twice as many children as any other ER MPH formulation [57].

The benefit of this management strategy was demonstrated in an 8-week, multicentre, open-label, randomized trial of OROS MPH, compared with usual care with IR MPH, in 147 children (aged 6–12 years) with ADHD who had significant after-school/evening behavioural difficulties [35]. Over the first 4 weeks of the study, subjects were titrated to a clinically effective dose of either study medication, and that dose was maintained for the remainder of the study. At the end of the study, subjects treated with OROS MPH experienced significantly higher remission rates than subjects treated with IR MPH (44 versus 16 % for the OROS MPH and IR MPH arms, respectively; $p = 0.0002$). These findings demonstrated that OROS MPH offers patients with ADHD and their families a treatment regimen that improves overall functioning and achieves normalization through symptom remission, reduced parental stress and improved socialization.

3.1 Comparison Studies

Several studies comparing OROS MPH with other long-acting formulations of MPH, with amphetamines or with atomoxetine have been published in the literature and are summarized in Table 1.

3.1.1 Studies Comparing OROS MPH with Other ER Formulations of MPH

Head-to-head comparisons using analogue classroom protocols over 8–12 h have shown that both OROS MPH and other long-acting MPH formulations offer benefits to children with ADHD. One study compared ER MPH 20 mg and OROS MPH 18 and 36 mg with placebo in a simulated school setting for the duration of an entire school day [58]. All three MPH arms outperformed the placebo arm over the first 4 h of the school day, as well as over the entire 8 h. Over the first 4 h, children in the ER MPH group had greater improvement in attention and behavioural ratings, and higher mathematics test scores, than children in both OROS MPH groups. Over the entire 8 h, children in the ER MPH group had greater improvement in deportment and combined ratings than those in the OROS MPH 18 mg group and were not different from those in the OROS MPH 36 mg group. Similar results were reported by Silva et al. [59], who compared ER MPH 20 and 40 mg with OROS MPH 19 and 36 mg. Up to 8 h postdose, improvements in SKAMP subscale scores and written mathematics test scores were significantly greater with ER MPH 40 mg than with OROS MPH 36 mg, while ER MPH 20 mg was equivalent to both doses of OROS

Table 1 Summary of studies published in the literature comparing the efficacy of osmotic-release oral system (OROS) methylphenidate (MPH) and other extended-release (ER) formulations of MPH, amphetamines or atomoxetine in children and adolescents

Study	Design	Population	Dosing	Findings
Studies comparing different formulations of ER MPH				
Lopez et al. [58]	4-way, randomized, single-blind, crossover, analogue classroom study (8 h school day) Assessments done on days 7, 14, 21 and 28	36 children (aged 6–12 years) with ADHD	ER MPH (20 mg/day), OROS MPH (18 or 36 mg/day) or placebo	All three MPH arms outperformed the placebo arm over the first 4 h of the school day, as well over the entire 8 h The ER MPH arm had greater improvement over the first 4 h on attention and behavioural ratings, and higher mathematics test scores, than both OROS MPH arms The ER MPH arm had greater improvement over the entire 8 h on deportment and combined ratings than the OROS MPH 18 mg arm and was not different from the OROS MPH 36 mg arm
COMACS (Swanson et al. [60])	Multicentre, double-blind, double-dummy, 3-way crossover, laboratory classroom study (13 h school day) Assessments done on days 7, 14 and 21	184 children (aged 6–12 years) with ADHD	ER MPH (20, 40 or 60 mg/day), OROS MPH (18, 36 or 54 mg/day) or placebo Dose selected on the basis of pre-existing dosing requirement for MPH	Both MPH arms outperformed placebo at all timepoints studied Superiority at any timepoint was achieved by the formulation with the highest expected plasma MPH concentration The ER MPH arm outperformed the OROS MPH arm in the early postdose period (1.5–4.5 h postdose) There was no difference between ER MPH and OROS MPH in the afternoon (6.0–7.5 h postdose) The OROS MPH arm outperformed the ER MPH arm in the evening (12 h postdose)
COMACS secondary analysis (Sonuga-Barke et al. [61])	Multicentre, double-blind, double-dummy, 3-way crossover, laboratory classroom study (13 h school day) Assessments done on days 7, 14 and 21	184 children (aged 6–12 years) with ADHD	ER MPH (20, 40 or 60 mg/day), OROS MPH (18, 36 or 54 mg/day) or placebo Dose selected on the basis of pre-existing dosing requirement for MPH Data analysed by high (ER MPH 60 mg or OROS MPH 54 mg), medium (ER MPH 40 mg or OROS MPH 36 mg) or low (ER MPH 20 mg or OROS MPH 18 mg) dose of MPH	Overall, ER MPH gave better control of ADHD symptoms from 1.5 to 6.0 h postdose Equivalent control of ADHD symptoms was achieved between 1.5 and 6.0 h postdose with lower doses of ER MPH (20 and 40 mg) and higher doses of OROS MPH (36 and 54 mg) Equivalent control of ADHD symptoms was achieved at 7.5 and 12.0 h postdose with lower doses of OROS MPH (18 and 36 mg) and higher doses of Metadate® CD (40 and 60 mg)

Table 1 continued

Study	Design	Population	Dosing	Findings
Silva et al. [59]	5-way, randomized, placebo-controlled, single-blind, crossover, laboratory classroom study (13 h day) Assessments done once weekly over 5 weeks	53 children (aged 6–12 years) with ADHD	ER MPH (20 or 40 mg/day), OROS MPH (18 or 36 mg/day) or placebo	All MPH arms outperformed placebo over the entire school day The efficacy of ER MPH 20 mg was similar to that of OROS MPH 18 and 36 mg in the first 8 h postdose The efficacy of ER MPH 40 mg was significantly greater than that of OROS MPH 36 mg in the first 8 h postdose All MPH arms demonstrated comparable efficacy from 8 to 12 h postdose
Muniz et al. [63]	Randomized, multicentre, double-blind, 5-period, crossover, laboratory classroom study (12 h day) Assessments done on days 7, 14, 21, 28 and 35	84 children (aged 6–12 years) with ADHD	ER dMPH (20 or 30 mg/day), OROS MPH (36 or 54 mg/day) or placebo	At 2 h postdose, a significant improvement in the SKAMP-Combined score was observed for the ER dMPH 20 mg group compared with the OROS MPH 36 mg group ($p < 0.001$) Both doses of ER dMPH demonstrated more rapid onset and greater morning effect, relative to OROS MPH OROS MPH demonstrated a greater benefit at the end of the 12 h classroom day
Silva et al. [64]	Randomized, multicentre, double-blind, 10-period, crossover, laboratory classroom study (12 h day) Assessment done on day 7 of each period	82 children (aged 6–12 years) with ADHD	ER dMPH (20 or 30 mg/day), OROS MPH (36 or 54 mg/day) or placebo	ER dMPH given at 20 mg was significantly more effective than OROS MPH given at 36 mg in improving SKAMP scores at 2 h postdose ER dMPH showed earlier onset of action in improving symptoms of ADHD than OROS MPH OROS MPH demonstrated a stronger effect in improving symptoms at 12 h postdose
COMACS subanalysis (Sonuga-Barke et al. [62])	Multicentre, double-blind, double-dummy, 3-way crossover, laboratory classroom study (13 h school day) Assessments done on days 7, 14 and 21	184 children (aged 6–12 years) with ADHD	ER MPH (20, 40 or 60 mg/day), OROS MPH (18, 36 or 54 mg/day) or placebo Dose selected on the basis of pre-existing dosing requirement for MPH	GMM was used to identify subgroups of children with ADHD from the COMACS study with different response profiles to different ER MPH formulations Children with more severe ADHD symptoms while on placebo had better response with both ER MPH and OROS MPH than children with less severe ADHD symptoms while on placebo OROS MPH was equally effective for all three classes of severity of ADHD symptoms ER MPH demonstrated a marked improvement in symptoms immediately after dosing in the two most severe classes compared with the least severe ER MPH showed greater symptom control than OROS MPH immediately after dosing

Table 1 continued

Study	Design	Population	Dosing	Findings
Studies comparing OROS MPH with amphetamine products				
Cox et al. [66]	Randomized, double-blind, placebo-controlled, crossover study	35 adolescents (aged 16–19 years) with ADHD	17-day course of OROS MPH (36 mg/day for 5 days, then 72 mg/day for 12 days) followed by 17-day course of MAS (15 mg/day for 5 days, then 30 mg/day for 12 days) or the reverse sequence	OROS MPH was associated with better driving performance than MAS and placebo ($p = 0.03$) Treatment with MAS demonstrated no improvement over placebo
Wilson et al. [65]	Randomized, double-blind, placebo-controlled, crossover study	35 adolescents (aged 16–19 years) with ADHD	17-day course of OROS MPH (36 mg/day for 5 days, then 72 mg/day for 12 days) followed by 17-day course of MAS (15 mg/day for 5 days, then 30 mg/day for 12 days) or the reverse sequence	Both OROS MPH and MAS significantly improved signs of impulsivity and memory compared with placebo No difference between OROS MPH and MAS in measurements of visual memory, attention span and response inhibition Significant improvement in neuropsychological functioning, measured by commission errors, reaction time and recall accuracy, was recorded with OROS MPH compared with placebo
Coghill et al. [67]	Randomized, double-blind, parallel-group, dose-optimized, placebo-controlled study	336 children (aged 16–12 years) and adolescents (aged 13–17 years) with ADHD	LDX (30, 50 or 70 mg/day), OROS MPH (18, 36 or 54 mg/day) or placebo over 7 weeks (4-week stepwise dose-optimization period, followed by 3-week maintenance period)	LDX showed a significant improvement in ADHD-RS total scores after 7 weeks of treatment, compared with placebo ($p < 0.001$, effect size = 1.80) OROS MPH showed a similar significant improvement, compared with placebo ($p < 0.001$, effect size = 1.26) 78 % of patients receiving LDX, 61 % of patients receiving OROS MPH and 14 % of patients receiving placebo achieved CGI-I scores of 1 or 2, at the end of the study OROS MPH had less than half the rate of discontinuation, relative to LDX, with the reported proportion of patients discontinuing treatment because of adverse events being 4.5 % for the LDX group, as compared with 1.8 % for the OROS MPH group and 3.6 % for the placebo group; it is likely that the difference in discontinuation rates (with LDX appearing to be more intolerable) and the difference in efficacy (with OROS MPH appearing to be less effective) was related more to noncomparable dosing of OROS MPH relative to LDX, and less to the absolute features of the drugs

Table 1 continued

Study	Design	Population	Dosing	Findings
Soutullo et al. [68] (post hoc analysis of Coghill et al. [67])	Randomized, double-blind, parallel-group, dose-optimized, placebo-controlled study	336 children and adolescents (aged 6–17 years) with ADHD	LDX (30, 50 or 70 mg/day), OROS MPH (18, 36 or 54 mg/day) or placebo over 7 weeks (4-week stepwise dose-optimization period, followed by 3-week maintenance period)	Treatment with LDX from baseline to the study endpoint resulted in significantly greater improvement in ADHD-RS scores than OROS MPH ($p < 0.001$) More patients treated with LDX achieved 30 % or greater reduction in ADHD-RS scores and CGI-I scores of 1 or 2 than patients treated with OROS MPH ($p < 0.05$ for both) The differences were more in keeping with limited dosing (OROS MPH reaching a maximal dose of 54 mg [not 72 mg] in comparison with LDX [reaching a maximal dose of 70 mg]), as noted above in the study by Coghill et al. [67]
Studies comparing OROS MPH with atomoxetine				
FOCUS (Kemner et al. [69])	3-week, prospective, open-label, multicentre study	1,323 children (aged 6–12 years) with ADHD	OROS MPH initiated at 18 mg/day, with dose titration over weeks 1 and 2 Atomoxetine initiated at 0.5 mg/kg/day, with dose titration over weeks 1 and 2	Subjects in the OROS MPH group experienced greater improvement in the ADHD-RS total score than subjects in the atomoxetine group ($p < 0.001$) Treatment response, measured as 25 % reduction from baseline ADHD-RS scores, was greater in the OROS MPH group than in the atomoxetine group ($p < 0.001$)
FOCUS subanalysis (Starr and Kemner [70])	3-week, prospective, open-label, multicentre study	183 African– American children (aged 6–12 years) with ADHD	OROS MPH initiated at 18 mg/day, with dose titration over weeks 1 and 2 Atomoxetine initiated at 0.5 mg/kg/day, with dose titration over weeks 1 and 2	Subjects in the OROS MPH group experienced greater improvement in the ADHD-RS total score ($p < 0.03$), as well as greater improvement on the inattentiveness subscale ($p < 0.02$), than subjects in the atomoxetine group More subjects in the OROS MPH group achieved ADHD-RS score reductions of ≥30 or ≥50 % from baseline, compared with the atomoxetine group ($p < 0.03$ for ≥30 % reduction and $p < 0.006$ for ≥50 % reduction) More subjects in the OROS MPH group achieved CGI-I scores ≤2 (i.e. 'very much improved' or 'much improved') than in the atomoxetine group ($p < 0.01$)
Newcorn et al. [71]	6-week, randomized, double-blind, placebo-controlled, parallel-design study	516 children and adolescents (aged 6–16 years) with ADHD	Atomoxetine (0.8–1.8 mg/kg/day), OROS MPH (18–54 mg/day) or placebo	Patients in both the atomoxetine and OROS MPH groups had markedly better response rates, defined as at least 40 % decrease in ADHD-RS total scores, than patients in the placebo group (45, 56 and 24 %, respectively) Patients in the OROS MPH group had a significantly better response rate than patients in the atomoxetine group ($p = 0.02$)

Table 1 continued

Study	Design	Population	Dosing	Findings
Yildiz et al. [72]	12-week, prospective, randomized, open-label study	30 children and adolescents (aged 8–14 years) with ADHD	OROS MPH (18 mg/day, with dose titration up to 36–54 mg/day) Atomoxetine (0.5 mg/kg/day, with dose titration up to 1.2 mg/kg/day)	Patients in the OROS MPH group achieved significantly greater reduction in teacher T-DSM-IV-S scores than patients in the atomoxetine group ($p < 0.005$) Patients in the OROS MPH group had greater improvement in time and number of corrections on the Stroop Test than patients in the atomoxetine group Subjects in the OROS MPH group showed a greater decrease in the percentage of perseverative errors on the WCST than subjects in the atomoxetine group ($p = 0.005$)

ADHD attention-deficit/hyperactivity disorder, *ADHD-RS* ADHD Rating Scale, *CGI-I* Clinical Global Impression—Improvement Scale, *COMACS* Comparison of Methylphenidates in the Analog Classroom Setting, *dMPH* dexmethylphenidate, *FOCUS* Formal Observation of Concerta versUs Strattera, *GMM* growth mixture modelling, *LDX* lisdexamphetamine, *MAS* mixed amphetamine salts, *SKAMP* Swanson, Kotkin, Agler, M-Flynn and Pelham Rating Scale, *T-DSM-IV-S* Turgay DSM-IV-Based Child and Adolescent Behavior Disorders Screening and Rating Scale (parent and teacher forms), *WCST* Wisconsin Card Sorting Test

MPH. From 8 to 12 h postdose, all active treatments demonstrated comparable efficacy. This difference is probably specific to nonequivalent doses, but it does suggest that OROS MPH may have benefit beyond bioequivalent doses of shorter-acting agents in association with duration of action.

The Comparison of Methylphenidates in the Analog Classroom Setting (COMACS) study was designed to compare the efficacy of ER MPH and OROS MPH in children with ADHD, who were assigned to treatment groups on the basis of their pretrial dosage, receiving either high (ER MPH 60 mg or OROS MPH 54 mg), medium (ER MPH 40 mg or OROS MPH 36 mg) or low (ER MPH 20 mg or OROS MPH 18 mg) doses of MPH, and then attended a laboratory school [60]. Teacher ratings of attention and deportment, and performance on a 10 min mathematics test, were used as surrogate measures of response. The ER MPH arm outperformed the OROS MPH arm in the early period (1.5–4.5 h) postdose, while the OROS MPH arm outperformed the ER MPH arm in the evening (12 h postdose). There was no difference between ER MPH and OROS MPH in the afternoon (6.0–7.5 h postdose). Further analyses from the COMACS study revealed that equivalent control of ADHD symptoms was achieved between 1.5–6.0 h postdose with lower doses of ER MPH (20 and 40 mg) compared with higher doses of OROS MPH (36 and 54 mg) [61]. When factoring in all doses for both treatments, ER MPH gave better overall control from 1.5 to 6.0 h postdose. Lower doses of OROS MPH (18 and 36 mg) and higher doses of ER MPH (40 and 60 mg) resulted in equivalent control at 7.5 and 12.0 h postdose. Sonuga-Barke et al. [62] used growth mixture modelling (GMM) to identify subgroups of children with ADHD from the COMACS study with different response profiles to different extended-release formulations of MPH. The study investigators observed that the more severe the symptoms were during placebo treatment, the better the children's response was for both ER MPH and OROS MPH. While OROS MPH was equally effective for all three classes of severity of ADHD symptoms, ER MPH demonstrated a marked improvement in symptoms immediately after dosing in the two most severe classes compared with the least severe. Thus ER MPH showed greater symptom control than OROS MPH immediately after dosing.

Muniz et al. [63] compared extended-release dexmethylphenidate (ER dMPH) at 20 and 30 mg with OROS MPH at 36 and 54 mg in children with ADHD in a laboratory classroom setting. At 2 h postdose, a significant improvement in SKAMP-Combined scores was observed for the ER dMPH 20 mg group compared with the OROS MPH 36 mg group ($p < 0.001$). Both doses of ER dMPH demonstrated a more rapid onset and a greater morning

effect, relative to OROS MPH, while OROS MPH demonstrated a greater benefit at the end of the 12 h classroom day. Silva et al. [64], studying the same doses of ER dMPH and OROS MPH, observed that ER dMPH 20 mg was significantly more effective than OROS MPH 36 mg in improving SKAMP scores at 2 h postdose. ER dMPH showed an earlier onset of action in improving symptoms of ADHD than OROS MPH, while OROS MPH demonstrated a stronger effect on improving symptoms at 12 h postdose. These findings show that superiority was achieved by the formulation with the highest expected plasma MPH concentration at that particular timepoint. No single formulation of MPH is superior to all others across all timepoints and across all measures of efficacy.

3.1.2 Studies Comparing OROS MPH with Amphetamine Products

Wilson et al. [65] compared the effects of OROS MPH and mixed amphetamine salts (MAS) on neuropsychological functioning among adolescents with ADHD who completed three separate assessments (at 5 p.m., 8 p.m. and 11 p.m.) on three different days and medications (OROS MPH, MAS and placebo). Visual memory, attention span and response inhibition were measured using the Delayed Matching-to-Sample Test and the Go/No-Go Test. Both treatments significantly improved signs of impulsivity and memory, compared with placebo. Moreover, significant improvement in neuropsychological functioning, measured by commission errors, reaction time and recall accuracy, was recorded with OROS MPH compared with placebo. This study was the first to suggest that OROS MPH improves not only symptomatic behaviours but also cognitive functioning. OROS MPH has also been shown to offer a greater benefit over MAS in terms of improving driving performance among adolescents with ADHD [66]. In this latter study, the performance of adolescent drivers with ADHD was compared on a driving simulator at 5 p.m., 8 p.m. and 11 p.m. after administration of OROS MPH 72 mg, MAS 30 mg or placebo at 8 a.m. OROS MPH resulted in better driving performance than placebo and MAS, while MAS demonstrated no improvement over placebo.

More recently, Coghill et al. [67] evaluated the efficacy of LDX and OROS MPH, compared with placebo, in children and adolescents with ADHD. Patients were treated with LDX 30, 50 or 70 mg or with OROS MPH 18, 36 or 54 mg daily. LDX showed a significant improvement in ADHD Rating Scale (ADHD-RS)-IV total scores after 7 weeks of treatment ($p < 0.001$), compared with placebo, with an effect size of 1.80. Treatment with OROS MPH resulted in a similar significant improvement, compared with placebo ($p < 0.001$), with an effect size of 1.26. Overall, 78 % of patients receiving LDX, 61 % of patients receiving OROS MPH and 14 % of patients receiving placebo achieved improvement, defined as a CGI-I score of 1 or 2, at the end of the study. Post hoc analysis of the data revealed that the difference between LDX and OROS MPH in terms of the mean change in the ADHD-RS-IV total score from baseline to the study endpoint was significant in favour of LDX ($p < 0.001$) [68].

Nevertheless, potential issues must be raised with the dosing comparison in the study, as the top dose of OROS MPH in the study was only 54 mg qd as opposed to a usual maximal dose of 72 mg. Thus the potential difference in efficacy between the two drugs might be attributable to differences in maximal dosing or noncomparable doses rather than to actual differences in efficacy. This is supported by the fact that patients who received LDX had more than double the rate of discontinuation due to adverse events, compared with those who received OROS MPH. With the reported proportion of patients discontinuing treatment due to adverse events being 4.5 % for the LDX group, as compared with 1.8 % for the OROS MPH group and 3.6 % for the placebo group, it is likely that the difference in the discontinuation rate (with LDX appearing to be more intolerable) and the difference in efficacy (with OROS MPH appearing to be less effective) was related more to noncomparable dosing of OROS MPH relative to LDX, and less to the absolute features of the drugs.

3.1.3 Studies Comparing OROS MPH with Atomoxetine

The Formal Observation of Concerta versUs Strattera (FOCUS) study [69] evaluated treatment outcomes with OROS MPH and atomoxetine among children with ADHD, using investigator-rated measures of symptoms, including the ADHD-RS and CGI-I. After 7 weeks of treatment, patients in the OROS MPH group and patients in the atomoxetine group had significant reductions in ADHD-RS scores from baseline. At the end of the study, the mean decreases in ADHD-RS scores were 20.24 for OROS MPH and 16.00 for atomoxetine, with the difference between treatments of 4.24 points being significant ($p < 0.001$). The differences between the two treatment arms increased over time and were 2.77, 3.44 and 4.24 at weeks 1, 2 and 3, respectively ($p < 0.001$). Treatment response, defined as a 25 % reduction in ADHD-RS scores from baseline, was significantly greater at each evaluation for patients in the OROS MPH group than for patients in the atomoxetine group ($p < 0.001$). A subanalysis of the FOCUS study was conducted to determine the effectiveness and tolerability of ADHD treatments among African–American patients [70]. The study investigators reported that, compared with patients in the atomoxetine group, patients in the OROS MPH group experienced greater improvement in the

ADHD-RS total score ($p < 0.03$), as well as greater improvement on the inattentiveness subscale ($p < 0.02$). More patients in the OROS MPH group achieved ADHD-RS score reductions of ≥30 or ≥50 % from baseline, compared with the atomoxetine group ($p < 0.03$ for ≥30 % reduction; $p < 0.006$ for ≥50 % reduction). In addition, more subjects in the OROS MPH group achieved CGI-I scores ≤2 (i.e. 'very much improved' or 'much improved'), compared with the atomoxetine group ($p < 0.01$). The findings of the FOCUS study suggest that OROS MPH offers greater ADHD symptom improvement than atomoxetine.

Newcorn et al. [71] conducted a study designed to compare the response to atomoxetine with the response to OROS MPH among children and adolescents with ADHD over 6 weeks. Response was defined as at least a 40 % decrease in the ADHD-RS total score. Although at the end of the study, patients in both the atomoxetine and OROS MPH groups had markedly better response rates than patients in the placebo group (45, 56 and 24 %, respectively), the OROS MPH group had a significantly better response rate than the atomoxetine group. In a more recent study, Yildiz et al. [72] compared the effects of atomoxetine and OROS MPH on executive functions in children with ADHD over 12 weeks. At the end of the study, patients in the OROS MPH group achieved significantly greater reductions in teacher Turgay DSM-IV-Based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-DSM-IV-S) scores than patients in the atomoxetine group. OROS MPH was more effective in improving time and number of corrections on the Stroop Test. In addition, patients in the OROS MPH group had a significant decrease in the percentage of perseverative errors on the Wisconsin Card Sorting Test (WCST), compared with patients in the atomoxetine group ($p = 0.005$). The findings of these studies demonstrate that although both OROS MPH and atomoxetine are effective in treating ADHD, greater improvement is offered by OROS MPH.

3.2 Summary

Long-acting OROS MPH appears to show benefits for children aged 6-12 years, with strong suggestions that it is more beneficial than equivalent doses of shorter-acting medications. This may be due to steady-state effects and benefits of activity lasting longer into the afternoon and evening. It should be noted that no one treatment appears superior to another across all domains studied and across all time points studied. Therefore, the selection of medication must be based on the individual requirements of each patient, to supply the optimum control of symptoms during the part of the day in which symptom control is the most essential. Nevertheless, given the likelihood of the benefit of MPH over amphetamine being equivalent to the likelihood of the benefit of amphetamine over MPH [73], as advocated by a multitude of treatment algorithms [8, 42, 43], a trial of both agents should be considered.

4 Review of Clinical Trials of Use of MPH in Adolescents (13–18 Years of Age): Focus on OROS MPH

In comparison with the wealth of information available from studies carried out in children with ADHD, few research studies have been published on the use of OROS MPH to treat adolescents with ADHD.

Wilens et al. [74] were the first to report the results of a multicentre trial evaluating the efficacy and tolerability of OROS MPH in adolescent subjects (aged 13–18 years) with ADHD. The study was undertaken in four phases. The first phase was a 1-week washout phase, the second phase was an open-label dose-titration phase lasting up to 4 weeks, the third phase was a 2-week, randomized, double-blind study, which compared individualized treatment with OROS MPH and placebo, and the fourth phase was an 8-week, open-label, follow-up safety study assessing treatment with OROS MPH at individualized doses. The starting dose of OROS MPH in the phase 2 dose-titration protocol was 18 mg/day. After approximately 7 days, the dose could be increased to 36 mg/day for subjects who did not achieve improvement in symptoms. Subjects were assessed weekly, and doses were increased, first to 54 mg/day and then to 72 mg/day, which was the maximum dose allowed in the study. Those subjects who did not demonstrate improvement at the maximum dosage discontinued their participation in the study. A total of 177 of the 220 subjects who entered into the study successfully completed the phase 2 dose-titration study and entered into the phase 3, double-blind, placebo-controlled part.

The authors reported that from baseline to the end of phase 3, treatment with OROS MPH, when compared with placebo, was associated with clinically significant improvements in the investigator-administered ADHD-RS score ($p = 0.001$), parent ADHD-RS score ($p = 0.008$), Parent–Child Conflict Index ($p = 0.005$) and subject Conners–Wells Adolescent Self-Report of Symptoms Scale score ($p = 0.001$) [74]. In addition, 52 % of subjects in the OROS MPH group scored 'much improved' or 'very much improved' on a CGI-I subscale, compared with 31 % of subjects receiving placebo. The most frequently reported treatment-related adverse events observed during the study included headache (25 %), decreased appetite (21 %), insomnia (15 %) and abdominal pain (9 %). During the double-blind phase, the incidence of drug-related adverse events was similar (18 % in the OROS MPH group versus

16 % in the placebo group). The findings of the study showed that OROS MPH reduced the symptoms of ADHD and was well tolerated up to dosages of 72 mg/day in adolescents.

Phase 4, the 8-week, open-label extension phase of the study, enrolled 171 of the 177 subjects (97 %) who were randomized to phase 3 of the study [75]. A total of 135 subjects (79 %) completed the 8-week, open-label extension phase. Of the subjects who did not complete the study, 12 (7 %) withdrew because of adverse events, 8 (5 %) withdrew because of protocol violations, 7 (4 %) were lost to follow-up, 6 (4 %) discontinued for unspecified reasons and 3 (2 %) discontinued because of lack of efficacy. Overall, 96 subjects (56 %) reported 189 adverse events during the open-label phase. Most subjects (92/96; 96 %) reported adverse events that were mild or moderate in severity. Investigators considered only 80 (42 %) of the 189 reported adverse events to be related to the study medication. Interestingly, there were no differences in the percentages of subjects reporting adverse events ($p = 0.480$) amongst the various OROS MPH dose groups (18 mg, 36 mg, 54 mg and 72 mg/day). The most frequently reported treatment-related adverse events across all OROS MPH dose groups were headache (12 %), anorexia/decreased appetite (8 %), insomnia (4 %) and weight loss (2.3 %). The results of this open-label extension study suggested that OROS MPH at doses from 18 to 72 mg/day is safe and well tolerated for the treatment of adolescents with ADHD.

Newcorn et al. [76] carried out a further subanalysis of the 4-week, escalating dose-titration phase of the study (originally reported by Wilens et al. [74]) in order to characterize the dose response and predictors of effective dosing in adolescents. The study investigators observed that the majority of subjects who did not respond at lower doses of OROS MPH did achieve a response when titrated to the next higher dose, with a dose of 54 mg/day or greater being required by approximately two thirds of the subjects. There was only a modest correlation between the minimal effective dose and baseline symptom severity, and no correlation between the dose and the variables of age, height and weight. As a result, the authors were able to show that adolescents required a higher absolute dose but a lower weight-adjusted dose (in milligrams per kilogram) of OROS MPH than the dose reported in children.

A 12-week, open-label study in 121 adolescents (aged 12–18 years) with ADHD investigated the effect of OROS MPH on learning skills [77]. Patients were administered flexible doses of OROS MPH, starting at 18 mg/day for those weighing <30 kg and 27 mg/day for those weighing ≥30 kg. Doses were increased by 9 or 18 mg increments approximately every 7 days, on the basis of the dose of previous medication, bodyweight, clinical symptoms and adverse events, to a maximum of 72 mg/day or 1.4 mg/kg/day. Over the course of the study, K-ARS and Clinical Global Impression—Severity Scale (CGI-S) scores significantly improved, with the K-ARS score decreasing from 27.70 to 11.65 ($p < 0.0001$) and the CGI-S score decreasing from 4.93 to 2.83 ($p < 0.0001$). In addition, the CGI-I score at week 12 was 'very much improved', 'much improved', 'minimally or somewhat improved' and 'not changed' in 18.7, 51.2, 22.3 and 4.1 %, respectively. Learning skills, measured using the Learning Skills Test (LST), also improved significantly on all subscales (self-control, participation, dealing with task, reading, writing, test taking and information processing; $p < 0.001$ for all). The mean total score on the LST improved from 168.88 at baseline to 207.22 at the end of 12 weeks ($p < 0.001$). This study was the first to demonstrate that OROS MPH was effective in enhancing learning skills among adolescents with ADHD.

Adolescents with ADHD are at high risk for driving accidents, and there is a significant amount of literature suggesting that their driving performance may improve with psychostimulant medication [78]. Cox et al. [79] reported on the impact of OROS MPH on driving behaviours among adolescents with ADHD in a double-blind, crossover study. The study compared seven subjects with ADHD and six subjects without ADHD, and it showed that the subjects with ADHD had more career driving accidents ($p < 0.04$), had more motor vehicle violations ($p = 0.059$) and performed worse on the driving simulator in the placebo condition ($p < 0.05$). Subjects with ADHD also demonstrated improved driving performance during MPH treatment ($p < 0.05$), rated themselves as driving more poorly in the placebo condition ($p = 0.05$) and tended to perceive their driving as better during MPH treatment ($p = 0.07$).

In a subsequent study, Cox et al. [80] investigated the effect of a single dose of OROS MPH on the driving performance of 12 adolescents with ADHD [80]. The subjects were observed on two separate occasions, once on OROS MPH and once without medication, while driving on a standard 16-mile road course incorporating rural, highway and urban streets. The authors found that inattentive driving errors were reduced while subjects were on medication (4.6 versus 7.8 errors; $p < 0.01$), with a positive correlation between the dose of OROS MPH and the improvement in driving performance ($p < 0.01$).

In a further study by Cox et al. [80], using a randomized, crossover, single-blind methodology, seven adolescents with ADHD drove a sophisticated driving simulator at 2 p.m., 5 p.m., 8 p.m. and 11 p.m. on two separate days, once when treated with OROS MPH and once when treated with IR MPH [78]. The authors reported that when subjects were treated with OROS MPH, they demonstrated less

variability and better driving performance ($p = 0.004$) than when they were treated with IR MPH, particularly in the evenings ($p = 0.01$). These data suggest that in comparison with IR MPH, OROS MPH reduced driving errors and improved the driving performance of adolescents with ADHD. Interestingly, this became increasingly important as the assessment went later into the evening, suggesting that OROS MPH is important in lowering the potential risk of driving errors in adolescents with ADHD, in comparison with IR MPH.

5 Review of Clinical Trials of Use of MPH in Adults (>18 Years of Age): Focus on OROS MPH

While ADHD has always been characterized as a childhood illness, it is estimated that ADHD affects 3.4–4.4 % of adults worldwide [2, 5, 81, 82]. Adult patients with ADHD experience impairment across multiple domains of daily living, including educational functioning and attainment, occupational functioning and failure to meet responsibilities at home [83]. In addition, like adolescents with ADHD, adults with ADHD show an increased risk of driving accidents, increased risk of alcohol and substance abuse, and a variety of psychiatric comorbidities. Currently in Canada and the USA, the stimulants MPH [23, 24], LDX [27, 28] and OROS MPH [21, 22], as well as the non-stimulant atomoxetine [25, 26], are approved to treat ADHD in adults. Although in Europe at present, MPH pellets are approved in Germany only to treat ADHD in newly diagnosed adults [20], there is approval for use of OROS MPH (as well as LDX) in adults with ADHD whose symptoms persist from adolescence into adulthood and who have shown clear benefit from treatment [18, 19]. In addition, atomoxetine is approved for use in adults with ADHD in Europe [84].

The safety and efficacy of once-daily OROS MPH was evaluated in the treatment of adults with ADHD in a randomized, 6-week, placebo-controlled, parallel-design trial undertaken in 141 subjects aged 19–60 years, who met full diagnostic criteria for DSM-IV ADHD [85]. OROS MPH or placebo was initiated at 36 mg/day and titrated to optimal response, depending on efficacy and tolerability, in increments of 36 mg/day up to 1.3 mg/kg/day. Dose titration was carried out only for subjects who failed to attain a CGI-I score of 1 or 2, or a reduction in the Adult ADHD Investigator System Report Scale (AISRS) score greater than 30 %, and who did not experience any untoward adverse effects. Subjects who were treated with OROS MPH experienced clinically and statistically significant reductions in symptoms of inattention and hyperactivity/impulsivity, in comparison with subjects treated with placebo. At the study endpoint, 66 % of subjects ($n = 44$) receiving OROS MPH and 39 % of subjects ($n = 23$) receiving placebo were 'much improved' or 'very much improved' on the CGI-I and achieved >30 % reduction in AISRS scores ($p = 0.002$). OROS MPH was not associated with worsening in symptoms of anxiety or depression. It was, however, associated with small increases in systolic blood pressure (3.5 ± 11.8 mmHg), diastolic blood pressure (4.0 ± 8.5 mmHg) and heart rate (4.5 ± 10.5 beats/min). The findings of this study demonstrated that treatment with OROS MPH in daily doses of up to 1.3 mg/kg/day was effective in the treatment of adults with ADHD; it also suggested that subjects receiving treatment with stimulants should be monitored periodically for changes in blood pressure.

In a separate, 6-week, open-label study with a similar dose escalation protocol, Biederman et al. [86] assessed the efficacy and safety of OROS MPH in adults with later-onset (after the age of 7 years) ADHD. As such, subjects were included in the study if they met full diagnostic criteria for DSM-IV ADHD Not Otherwise Specified (NOS) and were between 19 and 60 years of age. The study protocol provided for OROS MPH to be titrated from a starting dose of 36 mg/day at week 1 to 72 mg/day by week 2 and 108 mg/day by week 3. The dose was increased thereafter only for subjects who did not achieve a CGI-I score of 1 or 2, or who did not show a reduction of more than 30 % in the AISRS score. On the basis of tolerability and weight, the dose of OROS MPH was increased up to a maximum daily dose of 1.3 mg/kg/day. The study enrolled 36 subjects, of whom 29 (81 %) completed the trial. Patients received an average daily dose of 78.2 ± 29.4 mg of OROS MPH, which was associated with statistically and clinically significant reductions in ADHD symptoms, as assessed by the AISRS (−16.4 ± 10.5; $p < 0.001$). At the study endpoint, 26 subjects (72 %) were 'much improved' or 'very much improved' on the CGI-I. The results of this study supported the benefit of OROS MPH in ADHD-suffering adults who may have met criteria for later onset of their ADHD.

A subsequent 38-day, open-label study was designed to evaluate the safety, tolerability and efficacy of OROS MPH in providing core symptom control and improving executive function in adults (aged 18–65 years) with DSM-IV ADHD [87]. Executive function was assessed using the Stroop Color–Word Test (interference/response inhibition), Working Memory Index of the Wechsler Adult Intelligence Scale (WAIS)-III Test (working memory, attention) and Controlled Oral Word Association Test (COWAT) verbal and category (fluency). Subjects were eligible for the study if they had a baseline Conners Adult ADHD Rating Scale (CAARS) score ≥24, a CGI-S score ≥4 (at least moderate illness) and a Montgomery–Åsberg Depression Rating Scale (MADRS) score ≤16. The initial dose of OROS

MPH was 18 mg/day for 3 days, which was then titrated to 36 mg/day for 7 days. Thereafter, the dose was increased, depending on response, tolerability and the clinician's judgment, up to a maximum of 72 mg/day. At the end of the study, the mean daily dose of OROS MPH was 52.3 ± 14.0 mg/day. This was associated with a significant decrease in total CAARS scores, as well as decreases in the inattention ($p < 0.0001$) and hyperactivity/impulsivity symptom subscales ($p < 0.0001$). Executive function and all other secondary measures, including the CAARS Self-Report, CGI-S/CGI-I, Subject Satisfaction with Treatment and Sheehan Disability Scale scores were also significantly improved. Fallu et al. reported no serious adverse events, and none of the subjects discontinued medication because of an adverse event. The results of this study supported the findings of Biederman et al. [85] and showed that OROS MPH improves executive function in the areas of response inhibition, verbal/category fluency and working memory, all of which have been previously identified as having critical roles in adult ADHD [88].

The Long-Acting Methylphenidate in Adult ADHD (LAMDA) trial evaluated and compared the safety and efficacy of three fixed doses of OROS MPH in a large, 5-week, multicentre, double-blind, placebo-controlled study in adults with ADHD [89]. A total of 401 adult subjects (aged 18–65 years) were randomized to receive placebo ($n = 96$) or OROS MPH at either 18 mg/day ($n = 101$), 36 mg/day ($n = 102$) or 72 mg/day ($n = 102$), with efficacy assessed as the change in the total CAARS score at the study endpoint compared with baseline. Subjects in the OROS MPH arms experienced greater improvements in the CAARS score than subjects in the placebo arm. The mean changes in the CAARS score were 10.6 ($p < 0.01$), 11.5 ($p < 0.01$) and 13.7 ($p < 0.001$) for subjects treated with OROS MPH 18, 36 and 72 mg/day, respectively, compared with a 7.6-point improvement in the placebo arm. There were also more responders (defined as a ≥30 % decrease) in the OROS MPH groups (50.5, 48.5 and 59.6 % in the 18, 36 and 72 mg/day groups) as compared with the placebo group (27.4 %; $p < 0.001$), supporting the benefit of OROS MPH at fixed doses of 18, 36 and 72 mg/day in adults with ADHD.

In subsequent regression analyses of data from the LAMDA trial, CAARS hyperactivity/impulsivity subscale scores and CGI-S scores were shown to be highly interrelated with daily functioning, as assessed with the Sheehan Disability Scale ($p < 0.05$) [90]. These results showed that treatment with OROS MPH was associated with significant improvements in ADHD symptoms that directly related to improved daily functioning.

A 7-week, open-label extension of the LAMDA trial was carried out in 370 of the original 401 subjects who completed the double-blind phase or discontinued OROS MPH because of poor tolerability [91]. The extension study permitted a flexible dose regimen of OROS MPH, ranging from 18 to 90 mg/day for each patient, based on clinical responsiveness, with the starting dose of OROS MPH being either 18 or 36 mg/day. Dose titration was undertaken on the basis of clinical observations of response and tolerability, with dose changes allowed by 18 mg increments, to either increase the dose to improve efficacy or decrease the dose to improve tolerability. The maximum dose was set at 90 mg/day. Dose adjustments were allowed 7 days or more after the previous dose adjustment. The final doses of OROS MPH were 18 mg (for 8 % of subjects), 36 mg (for 29 % of subjects), 54 mg (for 34 % of subjects), 72 mg (for 20 % of subjects) and 90 mg (for 9 % of subjects). Subjects in the OROS MPH arm of the double-blind phase experienced a small improvement in CAARS scores after 1 week in the open-label phase and greater improvements at weeks 3 and 7 ($p < 0.001$ at weeks 3 and 7). Subjects in the placebo arm of the double-blind phase also showed improvement in CAARS scores at weeks 1, 3 and 7 ($p < 0.001$ at all three timepoints). Most adverse events were mild or moderate in severity.

In the post hoc analysis of the extension trial, a significant relationship was revealed between the changes in the CAARS hyperactivity/impulsivity subscale scores and improvements in Sheehan Disability Scale scores, and improvements in the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) scores at the end of the open-label extension trials [92]. These results demonstrated the relationship between improvements in ADHD symptoms in adults receiving OROS MPH and improvements in daily functioning and QoL.

LAMDA-II was a double-blind, randomized, placebo-controlled, multicentre study designed to evaluate the safety and efficacy of OROS MPH at either 54 mg/day ($n = 90$) or 72 mg/day ($n = 92$) among adults with ADHD [93]. Patients randomized to OROS MPH were started at a dose of 36 mg/day for the first week and then received either 54 or 72 mg/day for 12 weeks. Patients randomized to placebo ($n = 97$) received placebo for 13 weeks. At the end of the study, patients in the OROS MPH 72 mg/day group had significantly more improved mean CAARS–Screening Version (CAARS–O:SV) scores than patients in the placebo group ($p = 0.0024$), which was first observed at week 3 and maintained throughout the remainder of the study. There was no difference in mean CAARS–O:SV scores between the placebo group and the OROS MPH 54 mg/day group. The mean CAARS–O:SV inattention scores decreased significantly in both OROS MPH groups ($p < 0.05$ and $p < 0.001$ for the 54 and 72 mg/day groups, respectively), although CAARS–O:SV hyperactivity/impulsivity scores were significantly lower among patients in the 72 mg/day group only compared with placebo

($p < 0.05$). CAARS–Self-Report: Short Version (CAARS–S:S) scores decreased significantly in both OROS MPH groups compared with the placebo group ($p < 0.05$). Overall, 86.5 % of patients in the 54 mg/day group and 91.3 % of patients in the 72 mg/day group experienced at least one treatment-emergent adverse event, with the most common adverse events being headache (28.1 and 29.3 % for patients in the 54 and 72 mg/day groups, respectively), decreased appetite (19.1 and 28.3 % for patients in the 54 and 72 mg/day groups, respectively), dry mouth (13.5 and 21.7 % for patients in the 54 and 72 mg/day groups, respectively) and nausea (18.0 and 17.43 % for patients in the 54 and 72 mg/day groups, respectively). This study demonstrated that OROS MPH offered a greater benefit at a dose of 72 mg/day than at a dose of 54 mg/day in the treatment of adults with ADHD, and that these doses were well tolerated, supporting the extension of the dose range of OROS MPH to 72 mg/day in adults with ADHD.

Adler et al. [94] assessed the efficacy and safety of OROS MPH in the management of ADHD in adults in a randomized, 7-week, double-blind, placebo-controlled, dose-escalation, parallel-group study. The daily dose of OROS MPH was started at 36 mg and increased by increments of 18 mg every 7 days until a satisfactory individualized dose was achieved (36, 54, 72, 90 or 108 mg) on the basis of improvement in ADHD symptoms. A total of 229 subjects (aged 18–65 years) were randomized to treatment: 113 to the OROS MPH arm and 116 to the placebo arm. Subjects in the OROS MPH group experienced greater improvements in the symptoms of ADHD than subjects in the placebo arm, as measured by changes from baseline in the AISRS total score at the end of the study ($p = 0.012$). In addition, subjects in the OROS MPH arm had lower mean CGI-I scores at the end of the study ($p = 0.008$). There was a higher percentage of responders (defined as >30 % improvement in the AISRS score and a CGI-I score $\leq$2) in the OROS MPH arm than in the placebo arm (36.9 versus 20.9 %, respectively; $p = 0.009$). OROS MPH was well tolerated, and there were no serious treatment-related adverse events.

The recently published Concerta Quality of Life (CONQoL) study was designed to assess the effectiveness of OROS MPH on QoL in adults with ADHD over a 12-week treatment period [95]. Evidence from the literature suggests that adults with ADHD have worse QoL scores than control subjects and subjects with subthreshold ADHD, and that those with more severe symptoms of ADHD are likely to experience much lower QoL [96]. CONQoL was a multicentre, open-label trial involving 60 adult subjects with ADHD who received OROS MPH at a starting dose of 18 mg/day. After 8 days, the dose was increased to 36 mg/day, and this dose was maintained for 20 days. On day 28, the dose of OROS MPH could be increased to 54 mg/day, depending on clinical response. On day 56, the dose could be further increased to a maximum dose of 72 mg/day. All Adult ADHD Quality of Life Scale (AAQoL) subscale scores (productivity, psychological health, life perspectives and relationships) improved from baseline to week 4 ($p < 0.0001$), as did the total AAQoL score ($p < 0.0001$), and these improvements were maintained to week 12. In addition, there were significant reductions in CGI-I, Hamilton's Depression Rating Scale (HAM-D), State and Trait Anxiety Inventory (STAI) and Adult Self-Report Scale (ASRS) scores from baseline to week 12 ($p < 0.0001$). No serious adverse events were reported. This study was the first to demonstrate that treatment of adults with ADHD with OROS MPH could have significant effects on QoL. Of note, as well, were the specific reductions in both depression and anxiety scores in association with improved QoL in patients treated with OROS MPH.

The long-term efficacy of OROS MPH in adults with ADHD was investigated in a 34-week, three-phase, randomized, double-blind study [97]. Phase 1 was a 6-week, double-blind, randomized, parallel-design, placebo-controlled efficacy trial; phase 2 was a 24-week, double-blind continuation study including only responders (defined as subjects with >30 % improvement in the AISRS score and a CGI-I score $\leq$2) from phase 1 (double-blind conditions from phase 1 of the study were maintained into phase 2); and phase 3 was a double-blind, placebo-controlled, 4-week discontinuation study including only responders from phase 2. The aims of the study were threefold: (1) to determine whether adults with ADHD would respond to treatment with OROS MPH in the short term (6 weeks); (2) to determine whether the clinical response achieved at 6 weeks could be maintained out to 6 months; and (3) to determine whether ADHD symptoms would relapse with discontinuation of OROS MPH after 6 months of treatment and clinical response. There were 223 subjects included in phase 1 of the study (109 were randomized to OROS MPH and 114 to placebo); 96 subjects continued into phase 2 of the study (62 were randomized to OROS MPH and 34 to placebo), and 23 entered and completed phase 3 of the study (12 were randomized to OROS MPH and 11 to placebo). Patients who experienced relapse during phase 2 or 3 (defined as either a worsening of the phase 1 endpoint CGI-I score of $\geq$2 or a 15 % worsening in the AISRS score, relative to baseline, for two consecutive visits) exited the study. The starting dose of OROS MPH was 36 mg/day (1.3 mg/kg/day), and dose titration was carried out in 36 mg/day increments for subjects who did not achieve response and did not experience adverse events.

At the end of phase 1, the mean dose of OROS MPH was 78.4 $\pm$ 31.7 mg/day (0.97 $\pm$ 0.32 mg/kg/day), compared with 96.6 $\pm$ 26.5 mg/day (1.16 $\pm$ 0.19 mg/kg/day)

for the placebo group ($p < 0.0001$). A significantly higher percentage of subjects achieved a clinical response at the end of phase 1 in the OROS MPH group compared with the placebo group (62 versus 37 %, respectively; $p < 0.001$). These responders entered into phase 2 of the study and maintained their clinical response through 24 weeks of double-blind treatment. Interestingly, when treatment was discontinued in phase 3 of the study, there was no noted statistical difference in the rate of relapse between OROS MPH responders randomized to placebo and those randomized to continue active treatment (18 versus 0 %, respectively; $p = 0.1$) While this lack of difference was most likely found in direct relation to the smaller numbers of subjects remaining in phase 3, further investigation needs to be undertaken to examine the specific effects of long-lasting stimulants over longer periods of time.

The long-term safety of OROS MPH in adults with ADHD was investigated in a multicentre, open-label, dose-titration, flexible-dose study, which treated 550 subjects over 6 or 12 months [98]. The starting dose was 36 mg/day, with dose titration every 7 days in 18 mg increments until subjects achieved an efficacy threshold or reached the maximum dosage of 108 mg/day, or experienced adverse events that limited the ability to raise the dose. In addition, dose reductions in 18 mg increments were permitted for subjects who experienced difficulties with tolerating treatment. Subjects who were unable to tolerate the minimum dose of 36 mg/day discontinued participation in the study. For the purposes of data analysis, no distinction was made between subjects who received 6 months of treatment and those who received 12 months of treatment. Predefined criteria identifying changes of potential clinical importance included systolic blood pressure greater than 140 mmHg, diastolic blood pressure greater than 90 mmHg, pulse rate greater than 100 beats/min, or weight loss greater than 10 % of bodyweight, which were met by 9.6, 12.0, 10.2 and 11.2 % of patients, respectively. Overall, subjects experienced modest increases in the mean systolic blood pressure (2.6 mmHg), mean diastolic blood pressure (1.9 mmHg) and mean pulse rate (4.1 beats/min) from baseline to the final visit. The authors also reported that subjects experienced a mean weight loss of 2.3 kg during the same time period, and other than an increase in heart rate, no other clinically meaningful changes in laboratory values or electrocardiographic parameters were observed. The most common adverse events were decreased appetite (26.7 %), headache (24.0 %), insomnia (20.7 %) and dry mouth (14.7 %). The findings of this study indicate that OROS MPH dosages from 36 to 108 mg/day was well tolerated for up to 1 year in adults with ADHD.

In a uniquely designed study, Chronis-Tuscano et al. [99] investigated the effects of OROS MPH on parenting behaviours that were suspected to be deficient in mothers with ADHD. The authors hypothesized that during phase 1 of the study, when OROS MPH was titrated to its maximum effective dose over 5 weeks, increasing doses of OROS MPH would be associated with improvements in both maternal ADHD symptoms and parenting behaviours, relative to baseline. In addition, the authors hypothesized that during phase 2 of the study, when mothers were randomly assigned to receive placebo or their maximally effective dose for 2 weeks, discontinuation of OROS MPH would be associated with increases in ADHD symptoms and maladaptive parenting.

The authors reported that during phase 1 of the study, as predicted, with increasing doses of OROS MPH, mothers reported significant decreases in inattention ($p < 0.001$), hyperactivity/impulsivity ($p < 0.01$), inconsistent discipline ($p < 0.01$) and use of corporal punishment ($p < 0.005$), compared with baseline. Furthermore, during phase 2 of the study, for the mothers randomly assigned to OROS MPH, improvements were found in inattention ($d = 0.46$), hyperactivity/impulsivity ($d = 0.38$) and relatively inappropriate administration of corporal punishment ($d = 0.42$), compared with mothers randomized to placebo. Medium to large effects were observed for maternal improvements ($d = 0.52$), poor monitoring/supervision ($d = 0.70$) and inconsistent discipline ($d = 0.71$) in mothers randomized to medication compared with those randomized to placebo.

Clearly, the undesirable effects of ADHD in adults are not limited to the adults themselves. As reported by Chronic-Tuscano et al. [99], there is an important indication that symptoms in parents with ADHD may pose a risk of unexpected harm to their children. Furthermore, treatment of adults with ADHD with OROS MPH will provide potential benefit and a change in life trajectory not only for adults who suffer from ADHD but also for their children.

6 Review of Clinical Trials of Use of Generic Formulations of OROS MPH

Both Health Canada and the FDA have set forth guidelines for the development of generic drugs [100, 101]. In brief, generic drugs must demonstrate the same active ingredient, dosage form, strength, route of administration and conditions of use as those of the original drug [100]. More importantly, the generic drug must demonstrate bioequivalence to the original drug. At its Advisory Committee for Pharmaceutical Science and Clinical Pharmacology Meeting in April 2010, the FDA recommended using additional bioequivalence metrics for any second-entry ER MPH formulation to ensure therapeutic equivalence and interchangeability of these products [102]. Health Canada currently uses the following two criteria to determine

bioequivalence: (1) the area under the concentration–time curve (AUC) of the generic drug should be between 80 and 125 % of that of the name-brand medication; and (2) the C_{max} of the generic drug must be between 80 and 125 % of that of the name-brand medication [101]. In 2010, after expiration of the patent for Concerta®, Health Canada gave approval to Novopharm (now called Teva Canada; Toronto, ON, Canada) for a generic formulation of OROS MPH [103]. Marketed under the name Teva-Methylphenidate ER-C, it is available as 18, 27, 36 and 54 mg extended-release tablets [104]. A significant difference between Concerta® and Teva-Methylphenidate ER-C is that the latter falls under the Triplicate Prescription Program (TPP) of Alberta, Canada [105], which is designed to monitor all drugs with the potential for misuse/abuse and includes all MPH products, except for Concerta®, on the TPP list of medications [105].

Clinically significant differences may exist between different formulations of the same drug. In an effort to assess whether therapeutically relevant differences exist between bioequivalent formulations, Tothfalusi et al. [106] conducted a study in 16 healthy volunteers receiving 400 mg of carbamazepine.

The volunteers were divided into four groups, where each group received one of four carbamazepine formulations. Blood samples were taken over a period of 96 h, and adverse effects such as headache, dizziness, ataxia, diplopia, fatigue, drowsiness, nausea and abdominal pain were recorded. It was demonstrated that although the C_{max} ratios of 0.92, 1.03 and 1.07 fell within the criteria set forth by Health Canada, the corresponding maximum risk of experiencing an adverse event (R_{max}) ratios were 0.69, 1.23 and 1.46. An R_{max} value of 1.46 corresponds to a 46 % increase in the peak risk of toxicity, relative to the reference formulation. These results showed that clinically significant differences in toxicity, measured as increased risk of experiencing an adverse event, can exist between formulations that otherwise comply with bioequivalence requirements.

Other data have shown that patients may respond differently to a generic formulation of a drug compared with a brand-name drug formulation [107]. Mofsen et al. [108] reported seven case studies of patients who had been stabilized with brand-name clozapine and experienced a profound and rapid return of psychotic symptoms following a switch to a generic formulation. After brand-name clozapine was reinstated, all seven patients' symptoms resolved. Similar observations were made among 20 patients from an anxiety disorders clinic when they were switched from brand-name citalopram to a generic formulation [109]. These patients reported re-emergence of anxiety symptoms or development of adverse events after a mean time of 3.4 ± 1.6 weeks on the generic drug. All symptoms and adverse events had resolved at a mean of 3.8 ± 2.6 weeks after the patients switched back to brand-name citalopram. Rosenthal et al. [110] reported the sudden return of depressive symptoms among seven patients who had been switched from a brand-name antidepressant to a generic, or from their original generic to another generic, without their knowledge. Because these seven cases occurred over an extended period of time, the switch in medication was not immediately identified. As such, some patients' symptoms resolved following an adjustment in the dose of the generic drug, while other patients' symptoms resolved after they switched back to their previous medication.

To date, only two studies have compared the performance of brand-name OROS MPH and its generic version. The first study, by van Stralen [111], was a retrospective chart review of patients with ADHD. This study identified 162 patients who had been stabilized with OROS MPH, of whom 53 had switched to the generic version. Of the patients who switched, 45 (85 %) destabilized after the switch, and 22 (45 %) reported a shorter duration of effect. Of the patients who destabilized, 78 % stabilized back to their baseline when they were switched back to brand-name OROS MPH. The second study was a randomized, double-blind, crossover trial conducted in 20 adult patients with ADHD who were stable on OROS MPH for at least 3 months before being randomized to receive either OROS MPH or its generic formulation [112]. Significant differences were observed between OROS MPH and its generic formulation in the Treatment Satisfaction Questionnaire for Medication—Version II (TSQM-II) effectiveness ($p = 0.04$) and side effects ($p = 0.03$) subscales, with OROS MPH scoring better on both. These observations were supported by changes in AAQoL and physician-reported CGI-I and CGI-S scores. In addition, more adverse events were observed among patients when they were treated with the generic formulation. At the end of the study, all patients chose to return to OROS MPH. Although OROS MPH and its generic version are bioequivalent, there appear to be differences in terms of efficacy and adverse events. These observations warrant further investigation.

Although the studies by van Stralen [111] and Fallu and Daboux [112] showed differences between OROS MPH and its generic formulation, and patients preferred OROS MPH to the generic drug, this is not to say that patients cannot be successfully treated with a generic formulation of OROS MPH. Diagnosing, treating and stabilizing ADHD is a lengthy process. The studies discussed here demonstrate that once a patient has stabilized, it is of the utmost importance not to make changes to the treatment. If a patient is to be switched to another formulation, all individuals involved in the treatment plan (family/

physicians/pharmacists and regulators) should be aware of the possible effects of switching to another formulation.

7 Switching Studies

Of the stimulants used to treat ADHD, MPHs are the most well studied. Therefore, a lot of data have been generated for this type of medication, providing a good deal of evidence for its safety and efficacy, and therefore providing confidence for those who prescribe it. Remission rates for MPH in patients with ADHD have been reported to be in the range of 21–56 % for IR MPH [113, 114] and 44–62 % for OROS MPH [35, 60, 115, 116]. In comparison, the remission rate for atomoxetine is 27–30 % after 4–8 weeks of treatment, although it does increase up to 59 % after 12 weeks of treatment [117–119].

Several independent factors are believed to influence rates of remission, including the type and dose of medication, adherence to medication, ADHD subtype and presence of psychiatric comorbidities, as well as whether a behavioural intervention has been implemented [120, 121]. It is therefore not unexpected that patients and clinicians may need to switch from one medication to another as part of the treatment strategy to achieve remission. While it is not possible to ascertain to what extent treatment had been optimized prior to switching to OROS MPH, nor to what extent treatment optimization or closer observation after switching may have influenced patient outcomes, the following studies have reported the extent to which switching treatment to OROS MPH benefitted some patients.

7.1 Switching from IR MPH to OROS MPH

Remschmidt et al. [122] assessed the impact of switching from IR MPH to OROS MPH in 105 children and adolescents (aged 6–16 years) with ADHD who were stable on IR MPH at doses ranging from 10–60 mg/day. Subjects were switched to OROS MPH 18, 36 or 54 mg/day, on the basis of their prestudy IR MPH dose. After 3 weeks of treatment with OROS MPH, subjects who demonstrated benefit could continue in a 12-month extension period. A total of 101 subjects completed the 3-week treatment phase. At the end of the 3 weeks, parent/caregiver IOWA Conners Scale ratings decreased from baseline, particularly demonstrating an improvement in ADHD symptoms in the after-school period. Therapy with OROS MPH was rated as 'good' or 'excellent' by approximately 75 % of parents and investigators, with the treatment being reported to be well tolerated. The findings from this 3-week acute treatment phase of the study suggested that OROS MPH provided an added benefit to children and adolescents with ADHD who were stable on IR MPH, and offered improved symptom control and tolerability in the after-school period, after the switch to OROS MPH [122].

At the end of the 3-week treatment phase, 89 parents/caregivers (88.1 %) requested continuation in the 12-month extension phase, and 56 subjects (63 %) completed this phase [123]. During the extension phase, the parent/caregiver global assessment of satisfaction ranged from 49 to 69 %, and the treatment was rated as adequate by 49 to 71 % of investigators. Efficacy and satisfaction were greater among older subjects (aged 10–16 years), among subjects receiving a higher dose of OROS MPH (36 or 54 mg/day) and among subjects with a predominantly inattentive ADHD subtype. In addition, treatment with OROS MPH was well tolerated. This study was the first to report that children and adolescents could be effectively and safely switched from IR MPH to OROS MPH and could experience improved symptom control and compliance, and that this effect could be maintained for 12 months. Subsequently, similar results were reported by Chou et al. [115].

Kim et al. [124] evaluated the neurocognitive effects of switching from IR MPH to OROS MPH in 102 children with ADHD in a 28-day, open-label trial. The dose of OROS MPH was based on the prestudy IR MPH dose, where children receiving IR MPH 5, 10 and 15 mg tid were switched to OROS MPH 18, 36 and 54 mg/day, respectively. At the end of the study, subjects demonstrated significant improvements in the commission error and reaction time of both visual and auditory continuous performance tests (CPTs). In addition, improvements in parent/caregiver IOWA Conners Scale total scores were positively correlated with the reduction in commission error ($p < 0.001$) and with reductions in reaction time variability ($p < 0.006$) of visual CPTs. Despite the use of equivalent doses, these results supported the value of switching to longer-acting psychostimulants, and specifically switching from IR MPH to OROS MPH, in terms of specific associated improvements in neurocognitive performance in children with ADHD.

Clinical and health-related QoL (HRQoL) outcomes were assessed in a prospective, noninterventional study including 598 children and adolescents (aged 6–18 years) with ADHD who switched from IR MPH to OROS MPH on the basis of previously insufficient response and/or poor tolerability of IR MPH [125]. Twelve weeks after switching to OROS MPH, subjects demonstrated significant symptomatic, functional and HRQoL improvements as measured by Conners Parent Rating Scale, Children's Global Assessment Scale (CGAS) and Inventory for Assessing Quality of Life (ILC) LQ0–28 scores ($p < 0.0001$ for all comparisons). When asked to rate the effectiveness of OROS MPH and their satisfaction with

treatment, over 70 % of parents and physicians rated the effectiveness as being at least 'good' and were at least 'satisfied'. The most common adverse events related to treatment were insomnia and anorexia. No clinically relevant changes in bodyweight or vital signs were observed, and there were no significant changes in the quality of sleep or appetite.

Ramos-Quiroga et al. [31] conducted a study in adults with ADHD to investigate whether switching from IR MPH to OROS MPH increased drug adherence and resulted in improved effectiveness and tolerability. A total of 70 subjects participated in the study. During the first 3 months of the study, subjects were treated with IR MPH tid, with dose titration taking place over the first few days of treatment until a target dosage of 1.0 mg/kg/day was reached. Patients who did not tolerate this target dosage had their dosage lowered. After 3 months, subjects were switched to once-daily OROS MPH, where the dose was converted as follows: a 15 mg dose (5 mg tid) of IR MPH was substituted with an 18 mg dose of OROS MPH. Switching from IR MPH to OROS MPH was associated with a significant improvement in all items of the Simplified Medication Adherence Questionnaire, indicating better adherence for the OROS MPH arm. Overall, OROS MPH was more effective in reducing symptoms of ADHD ($p = 0.0005$) than IR MPH, and the percentage of responders (defined as ≥30 % improvement in their ADHD-RS-IV score, compared with baseline) was higher in the OROS MPH arm than in the IR MPH arm (91.4 versus 28.6 %, respectively; $p = 0.0005$). Moreover, OROS MPH was preferred to IR MPH by 97 % of subjects. The most common adverse event for IR MPH was dry mouth (30 %), whereas for OROS MPH it was mood instability (31 %). However, no subjects discontinued treatment because of adverse events. This study was the first to show that switching from IR MPH to OROS MPH was associated with both improved adherence and effectiveness. These findings were supported by Spencer et al. [126], who demonstrated that adults with ADHD can be successfully switched from an effective regimen of IR MPH to OROS MPH, resulting in better compliance with OROS MPH.

7.2 Switching from ER MPH to OROS MPH

Wolff et al. [127] investigated the clinical outcomes of children and adolescents (aged 6–18 years) with ADHD who had insufficient clinical response and/or poor tolerability of ER MPH and thus were switched from ER MPH to OROS MPH. A total of 180 subjects were included in this prospective, noninterventional, natural practice study, which followed subjects for 12 weeks after they switched to OROS MPH. At the end of 12 weeks of treatment with OROS MPH, changes in several symptomatic and functional outcomes from baseline were observed. There were decreases in Conners Parent Rating Scale scores ($p < 0.0001$) and increases in CGAS scores ($p < 0.0001$) and both parents' and patients' ILC LQ0–28 scores (both $p < 0.0001$). In addition, there were improvements in behaviour and, specifically, social interactions, playing with other children, doing household chores, doing school homework and going to bed ($p < 0.0001$). Overall, 72.8 % of subjects expressed satisfaction with OROS MPH therapy compared with their previous ER MPH therapy. OROS MPH was well tolerated, with approximately 40 % of patients reporting better sleep quality and appetite ($p < 0.0001$) after having switched from ER MPH. The most common adverse events reported were tics (8.9 %), insomnia (7.2 %) and anorexia (5.0 %). No significant changes in bodyweight or vital signs were observed. These data demonstrated that children and adolescents experienced improved functionality, improved symptom control and a decreased burden of disease after having switched from ER MPH to OROS MPH.

7.3 Switching from Atomoxetine to OROS MPH

The clinical outcomes of 42 children and adolescents (aged 6–18 years) with ADHD who had insufficient clinical response and/or poor tolerability of atomoxetine and who were switched to OROS MPH were assessed in a prospective, noninterventional study [128]. After switching to OROS MPH, subjects were followed for 12 weeks. At the end of 12 weeks of treatment with OROS MPH, changes in several symptomatic, functional and HRQoL outcomes from baseline were observed. There were decreases in Conners Parent Rating Scale scores ($p < 0.0001$) and increases in CGAS scores ($p = 0.0015$) and both parents' and patients' ILC LQ0–28 scores ($p = 0.0002$ and $p = 0.0003$, respectively). In addition, there were improvements in social interactions and late afternoon tasks, including playing with other children, household chores, school homework and behaviour ($p < 0.001$). With regard to symptom control in the late afternoon, 62 % of subjects rated their satisfaction with OROS MPH as 'very good' or 'good', compared with their prior atomoxetine therapy. The most common adverse events related to treatment were tics (16.7 %), insomnia (14.3 %), abdominal pain (9.5 %) and headache (9.5 %). No significant changes in bodyweight or vital signs were reported. These findings demonstrated that, after switching to OROS MPH from atomoxetine, children and adolescents experienced improvement in ADHD symptoms, as well as a positive QoL impact (as measured by HRQoL) and their disease burden.

8 Combination Studies

Although monotherapy with psychostimulants can achieve response rates of up to 70 %, a number of patients have inadequate or partial responses, or experience dose-limiting side effects [129]. Although there is little evidence in the literature documenting the use of combination or augmentation strategies in the treatment of ADHD, one retrospective claims database review found that combination therapy was present in 19.7 % of continuing months (i.e. months after the first month of therapy) for atomoxetine, 21.0 % for long-acting stimulants, 27.4 % for intermediate-acting stimulants, 23.1 % for short-acting stimulants, 36.9 % for bupropion and 53.0 % for α_2-adrenergic agonists [130]. Furthermore, the results of one small case series in four subjects have been published and reported a favourable outcome of combination therapies [131].

A two-phase, 7-week, open-label study in children and adolescents (aged 6–17 years) with ADHD who were partial responders (defined as having a CGI-I score $\leq$2) to atomoxetine assessed the effectiveness and tolerability of adding OROS MPH to the treatment regimen [132, 133]. In phase 1 of the study, subjects initiated treatment with atomoxetine for a minimum of 4 weeks. Fifty subjects who were partial responders to atomoxetine entered into phase 2 of the study and had OROS MPH added to atomoxetine therapy, and they were followed for an additional 3 weeks. A total of 41 subjects (82 %) completed the study. From the start of phase 2 through to the end of the study, subjects experienced a 40 % reduction in their ADHD-RS scores, as well as reductions in CGAS scores ($p < 0.0001$) [133]. In addition, there were also improvements in executive functioning. The most common adverse events reported among subjects prior to entering phase 2 of the study, and therefore associated with atomoxetine monotherapy, were mild-to-moderate gastrointestinal effects, fatigue and headache [132]. Compared with atomoxetine therapy alone, adjunctive OROS MPH therapy was associated with greater rates of mild to moderate insomnia ($p < 0.001$), irritability ($p = 0.02$) and loss of appetite ($p < 0.001$), and lower rates of fatigue ($p < 0.0005$). No change in weight was observed during atomoxetine monotherapy. However, there was a mean weight decline of 1.8 pounds with combined treatment ($p < 0.005$). These results suggest that OROS MPH, as an adjunct to treatment with atomoxetine in ADHD patients who are partial responders to atomoxetine, improves the symptoms of ADHD, as well as executive functioning [133]. However, over the short term of phase 2 of this study, the combined treatment resulted in an additive adverse effect burden, suggesting the need for further controlled studies [132].

9 Comorbidities

ADHD is often accompanied by comorbid psychiatric disorders, with the most common ones being oppositional defiant disorder (ODD), conduct disorder (CD), anxiety disorders, mood disorders, learning disabilities, tics and substance abuse disorders [134–136]. ODD and CD are present in approximately 50 % of children with ADHD [137] and have received a great deal of attention. As such, there is a plethora of studies in the literature addressing treatment of ADHD and comorbid ODD or CD. In comparison, there is very little published in the literature on the subject of ADHD with comorbid anxiety, despite the fact that these disorders are comorbid in approximately 25 % of children [137] and up to 50 % of adults with ADHD [2]. For a review on the subject of ADHD and comorbid bipolar disorder, see Klassen et al. [138].

9.1 Comorbid ODD or CD

Evidence from the literature demonstrates that treatment with MPH for the core symptoms of ADHD is as effective for individuals with comorbid disruptive behaviour disorders as it is for those without [139, 140]. Moreover, treatment with MPH results in significant improvement in symptoms of ODD and aggressive behaviour in patients with ADHD [141–143].

Steele et al. [35] investigated the efficacy and tolerability of OROS MPH versus IR MPH in children with ADHD. Although the study population did not specifically include children with ADHD and comorbid ODD, the study did assess the severity of ODD symptoms. Treatment with OROS MPH was superior to IR MPH in achieving remission on the basis of improvements in the severity of ADHD and ODD symptoms ($p = 0.004$). OROS MPH and IR MPH were both well tolerated and had similar adverse event profiles. This study demonstrated that OROS MPH was more effective and therefore of more value in the treatment of comorbid ADHD and ODD than IR MPH, resulting in increased rates of remission in these children.

Kronenberger et al. [144] assessed the impact of addition of quetiapine in adolescents with comorbid ADHD, CD/ODD and aggression who were incompletely responsive to MPH monotherapy alone. Subjects were initiated on treatment with OROS MPH at 18 mg/day for 1 week, with 18 mg increments every week until a maximum dose of 54 mg/day was achieved. At the end of the dose-titration period, subjects who did not meet the criteria for clinically significant improvement continued into the next phase of the study, which was a 9-week quetiapine addition treatment period. Quetiapine was initiated at 25 mg twice daily (bid) and could be increased according to the following schedule: 50, 100, 200, 300 mg bid. The dosage was

increased on the basis of efficacy and tolerability. The dosage was not increased, or was reduced, if clinically significant improvement criteria were met and/or if adverse events were deemed to preclude a dose increase. During the OROS MPH monotherapy phase, as well as during the combined OROS MPH–quetiapine treatment phase, ADHD symptoms, aggression and global functioning improved significantly. At the end of the combined treatment phase, 42 % of subjects met all criteria for clinically significant improvement and 79 % of subjects exhibited minimal aggression. This study demonstrated that addition of quetiapine to OROS MPH was effective in adolescent subjects with ADHD and comorbid CD/ODD.

Reimherr et al. [145] conducted a double-blind, crossover study in 47 adults with ADHD, where over 80 % of the subjects had ADHD with a combination of emotional and/or oppositional symptoms. Subjects were randomly assigned to receive either placebo or OROS MPH for 4 weeks. At the end of this period, subjects were crossed to the other treatment arm for an additional 4 weeks. OROS MPH treatment was started at 18 mg/day, with 9 mg increments every 2–3 days, on the basis of response and tolerance, up to a maximum dose of 90 mg/day. Once a patient was evaluated as being 'much improved' or better on the CGI-I, or improved by 50 % on the Wender–Reimherr Adult Attention Deficit Disorder Scale (WRAADDS), the dose of OROS MPH was maintained for the remainder of the 4-week block. Treatment with OROS MPH was found to be superior to placebo for all clinical measures. OROS MPH was associated with a 42 % decrease in the total WRAADDS score, compared with a 13 % decrease observed with placebo ($p < 0.001$), as well as a decrease of 41 % in the ADHD-RS total score, compared with a 14 % decrease with placebo ($p = 0.003$). This study demonstrated that OROS MPH was effective in treating adult ADHD where most subjects had ADHD with a combination of emotional and/or oppositional symptoms.

Marchant et al. [146] reported the results of a 6-month, open-label extension of the study by Reimherr et al. [145]. Of the 41 patients who completed the double-blind, crossover study, 34 continued into this open-label phase. During the open-label phase, the dosing of OROS MPH was not restricted, and dose adjustments were made to maximize improvement in ADHD symptoms while limiting adverse events. The WRAADDS-defined ADHD dimensions of attention + disorganization, hyperactivity + impulsivity and emotional dysregulation [ED] improved to similar extents (by 61, 60 and 66 %, respectively). All ADHD subgroups (ADHD alone, ADHD + ED and ADHD + ED + ODD) demonstrated improvement, although the ADHD + ED + ODD group experienced the most long-term improvement in this area. The findings of this 6-month extension study show that OROS MPH can successfully be used to maintain improvement in ED and oppositional symptoms in adults with ADHD.

9.2 Comorbid Substance Abuse

ADHD is highly prevalent in populations with substance use disorders and is associated with more severe outcomes [147, 148]. Some evidence from the literature has suggested that treatment with MPH leads not only to reductions in symptoms but also to a reduction in drug use [149–151]; other studies have not supported those findings [152, 153]. Riggs et al. [154] assessed the efficacy and safety of OROS MPH in the treatment of adolescents with ADHD and comorbid substance use disorders. This 16-week, randomized, placebo-controlled, multicentre study included 303 adolescents (aged 13–18 years) who were concurrently receiving cognitive behavioural therapy (CBT) for substance use disorders. Interestingly, no differences were observed between the OROS MPH group and the placebo group in terms of reduction in ADHD-RS (adolescent informant) scores, or reduction in days of substance use. Subjects in the OROS MPH group, however, did have lower ADHD-RS (parent informant) scores at 8 weeks ($p = 0.0163$) and 16 weeks ($p < 0.001$), and had more negative weekly urine drug screens ($p = 0.04$) than subjects in the placebo group.

Biederman et al. [155] reported that a lifetime history of a substance use disorder was a potential moderator of the dose of OROS MPH. In this three-phase, double-blind, placebo-controlled, parallel-design study of OROS MPH in adults (aged 19–60 years) with ADHD, phase 1 was a 6-week acute efficacy trial, phase 2 was a 24-week, double-blind continuation study of responders (defined as those with a >30 % improvement in AISRS scores and a CGI-I score ≤2) from phase 1, and phase 3 was a double-blind, placebo-controlled, 4-week discontinuation study. At the end of the study, the dose of OROS MPH was higher in subjects with ADHD and a history of substance abuse than in those with ADHD alone ($p = 0.04$). The study investigators suggested that the neurobiological underpinnings of substance use or prior exposure to alcohol and drugs may result in lower sensitivity to treatment with OROS MPH. These results warrant further investigation, but at present no firm conclusion can be drawn.

9.3 Comorbid Tics

According to a community-based study, 27 % of children with ADHD also have tic disorders, and 55 % of children with tic disorders also have ADHD [156]. Similar results have been reported in a school-based community sample [157]. It is believed that ADHD and tic disorders share a common pathophysiology involving alterations in

noradrenergic and dopaminergic transmission, inadequate modulation of corticostriatal circuits, and failure to inhibit intrusive thoughts, sensory input and motor responses [158]. Early studies on the use of stimulants in the treatment of children with ADHD found that MPH appeared to induce or worsen tics [159–162]. Still, it has been suggested that this relationship is temporal and not causal [157]. More recent studies assessing the safety and efficacy of MPH in the treatment of ADHD with comorbid tic disorders have demonstrated that the occurrence of tics either remained the same or improved [157, 163].

Palumbo et al. [164] evaluated whether OROS MPH was responsible for inducing or exacerbating tics in children with ADHD. In this analysis, data from five clinical studies were included: three placebo-controlled studies [32, 44, 45], one open-label study assessing the safety and efficacy OROS MPH in children [50] and one open-label study assessing the safety and efficacy of OROS MPH in children, adolescents and adults (data not previously published). For all of these studies, subjects with ADHD could enrol if they had mild to moderate tics, but subjects with Tourette's syndrome were not included.

The pooled analysis from the three placebo-controlled studies demonstrated that the incidence of tics was not significantly different between subjects treated with OROS MPH, IR MPH or placebo (4.0, 2.3 and 3.7 %, respectively; $p = 0.525$). During the first year of the 2-year open-label study, the incidence of tics was stable at approximately 5 %. There was no correlation between the OROS MPH dose and the frequency of tic episodes. These findings suggest that OROS MPH is not associated with the onset or worsening of tics in children with ADHD.

10 Conclusions

Clinical studies in children with ADHD treated with OROS MPH at doses ranging from 18 to 54 mg/day (and in comparison with placebo) have demonstrated significant improvements in symptomatic assessments of ADHD [44, 45, 52–54]. These include improvements in teacher and parent ratings of inattention/overactivity and oppositional/defiant behaviour [44]. In addition, significant reductions in core ADHD symptoms have been observed with OROS MPH, as measured by the teacher and parent IOWA Conners Scale [45], and improvements in performance on academic, behavioural and cognitive tasks [52–54] and different domains of attention and executive functioning [53, 54] have all been well documented. Moreover, OROS MPH has been shown to be superior to IR MPH in improving parent ratings of inattention/overactivity [44].

The greatest benefit of OROS MPH, however, lies in its ability to offer symptomatic control not only during the traditional school day (or during the work day in adults) but also after school or work, in the evening [55]. Compared with placebo, OROS MPH was associated with improvements in attention and behaviour that were sustained during the school day as well as during the late afternoon and during homework time [32, 44, 57], and better symptom control, in comparison with IR MPH, especially in the evening period [35].

In addition to its desirable efficacy, OROS MPH has a good safety profile. Studies evaluating the safety and tolerability of OROS MPH over 24 months in children have shown that OROS MPH is well tolerated, with an adverse event profile at least as good as that of IR MPH [49].

In the adolescent population with ADHD, treatment with OROS MPH at doses ranging from 18 to 72 mg/day is associated with significant improvements in investigator and parent ADHD-RS scores, Parent–Child Conflict Index scores and subject Conners–Wells Adolescent Self-Report of Symptoms Scale scores, when compared with placebo [74]. In addition, OROS MPH improves driving performance and reduces inattentive driving errors in adolescent drivers [80]. Compared with IR MPH, OROS MPH treatment in adolescent drivers was associated with less variability and better driving performance, particularly in the evening [78]. OROS MPH dosages of up to 72 mg/day appear to be safe and well tolerated in adolescents [75].

OROS MPH has been studied in adults with ADHD at doses ranging from 36 to 108 mg/day [85, 89, 94]. Compared with placebo, OROS MPH treatment in adults was associated with improvements in CAARS scores, as well as clinically and statistically significant reductions in symptoms of inattention and hyperactivity/impulsivity, as measured with the CGI-I and AISRS [85, 89, 94]. OROS MPH is also associated with improvements in QoL, maternal ADHD symptoms and parenting [95, 99]. These findings have shown that adults with ADHD benefit from treatment with OROS MPH and experience improvements in ADHD symptoms and daily functioning. Treatment with OROS MPH for up to 1 year has been well tolerated in adults at doses of up to 108 mg/day [98].

Psychostimulants form the cornerstone of treatment for ADHD, and MPH is recommended as first-line therapy in many countries [165]. MPH is believed to exert its effects in the dopaminergic circuits in the prefrontal cortex [166] by binding and inhibiting the dopamine transporter, which is responsible for the reuptake of dopamine from the synaptic cleft back to the presynaptic neuron [167]. Through inhibition of the dopamine transporter, MPH increases the level of dopamine in the synapse, which leads to an increase in both the magnitude and the duration of the dopaminergic signal. OROS MPH provides an additional benefit of maintaining MPH levels within the therapeutic range throughout the day and early evening, thereby

maintaining beneficial changes in prefrontal activity over an extended period of time. Moreover, avoiding peaks and troughs in dosing also avoids the effect of repeatedly moving from high, and potentially toxic, doses to subtherapeutic levels. OROS MPH was specifically designed with an ascending drug delivery profile to overcome the problem of tachyphylaxis (acute tolerance), which has been observed with short-acting MPHs and is believed to be the result of a nonascending drug delivery profile [32]. Indeed, adverse events associated with IR MPH increase linearly with the dose and commonly include insomnia, nervousness, irritability, anxiety, jitteriness, headache, stomach ache and anorexia [168]. A small study published by Stevens et al. [169] found no correlation between plasma MPH concentrations and the OROS MPH dose or changes in vital signs 4–5 h after administration. In this study, the mean plasma MPH concentration was 28 ± 9.1 ng/mL, despite a mean daily OROS MPH dose of 169 ± 5 mg (3.0 ± 0.8 mg/kg/day). Moreover, no patient was found to have a plasma MPH level >50 ng/mL or clinical signs of stimulant toxicity.

In addition, providing symptom control in the afterschool and evening periods is key to the development of personal and social skills in children [55]. Controlling symptoms of ADHD in the evening in children is associated with improved overall functioning and achieves normalization through symptom remission, reduction in parental stress and improved socialization [35]. Although no studies have specifically examined the effect of ADHD symptom control in adolescents and adults in the afterschool and evening periods, it is reasonable to assume that these patients experience benefit. Adolescents with ADHD, for example, who achieve symptom control after school and in the evening would be expected to be able to concentrate on homework and participate in extracurricular activities, much like children with ADHD who achieve symptom control during these periods [55]. In addition, adolescents with ADHD treated with OROS MPH demonstrate improved driving performance [78, 80]—an activity that presumably takes place both during the day and in the evening. By reducing the risk of driving accidents, both adolescent drivers and society benefit. In adults with ADHD, OROS MPH is associated with improved QoL, as measured by the AAQoL score, which assesses productivity, psychological health, life perspectives and relationships [95]. Presumably, improvements in these measures are influenced by symptom control in both the daytime and evening. In mothers with ADHD, OROS MPH is associated with improved parenting behaviour, which takes place both during the day and in the afternoon and evening, when children are home from school. Improved QoL and parenting behaviour benefit both the patient with ADHD and the family.

In conclusion, studies examining the efficacy of OROS MPH in children, adolescents and adults have demonstrated its significant efficacy and safety over the full day, as well as its benefit to patients with ADHD over IR MPH and ER MPH.

Acknowledgments The authors would like to thank Angela Styhler, MSc, for her assistance in the preparation of this paper, and for her assistance with the fact finding, etc., associated with the development of this manuscript. Funding related to this paper was received as part of an unrestricted educational grant from Janssen Inc.

Dr Katzman is the primary owner of the START Clinic for Mood and Anxiety Disorders.

Ms Sternat, MPsy, has been undertaking her research as part of her graduate training at the START Clinic for Mood and Anxiety Disorders. Ms Sternat is also an employee of Janssen Inc.

References

1. Dulcan M. Practice parameters for the assessment and treatment of children, adolescents, and adults with attention-deficit/hyperactivity disorder. American Academy of Child and Adolescent Psychiatry. J Am Acad Child Adolesc Psychiatry. 1997;36:85S–121S.
2. Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry. 2006;163:716–23.
3. Wender PH, Wolf LE, Wasserstein J. Adults with ADHD. An overview. Ann N Y Acad Sci. 2001;931:1–16.
4. Willcutt EG. The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. Neurotherapeutics. 2012;9:490–9.
5. Modesto-Lowe V, Meyer A, Soovajian V. A clinican's guide to adult attention-deficit hyperactivity disorder. Conn Med. 2012;76:517–23.
6. Remschmidt H. Global consensus on ADHD/HKD. Eur Child Adolesc Psychiatry. 2005;14:127–37.
7. Bond DJ, Hadjipavlou G, Lam RW, McIntyre RS, Beaulieu S, Schaffer A, et al. The Canadian Network for Mood and Anxiety Treatments (CANMAT) Task Force recommendations for the management of patients with mood disorders and comorbid attention-deficit/hyperactivity disorder. Ann Clin Psychiatry. 2012;24:23–37.
8. Pliszka S. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2007;46:894–921.
9. Ryan-Krause P. Attention deficit hyperactivity disorder: part III. J Pediatr Health Care. 2011;25:50–6.
10. Taylor E, Dopfner M, Sergeant J, Asherson P, Banaschewski T, Buitelaar J, et al. European clinical guidelines for hyperkinetic disorder—first upgrade. Eur Child Adolesc Psychiatry. 2004;13(Suppl 1):I7–30.
11. Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management, Wolraich M, Brown L, Brown RT, DuPaul G, et al. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics. 2011;128:1007–1022.
12. National Institute for Health and Clinical Excellence (NICE). Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents. http://guidance.nice.org.uk/TA98. Accessed 29 Jan 2014.

13. Canadian Attention Deficit Hyperactivity Disorder Resource Alliance (CADDRA). Canadian ADHD nes. http://www.caddra.ca/practice-guidelines/download. Accessed 29 Jan 2014.
14. Scottish Intercollegiate Guidelines Network (SIGN). Management of attention deficit and hyperkinetic disorders in children and young people. http://sign.ac.uk/guidelines/fulltext/112/index.html. Accessed 29 Jan 20.
15. Banaschewski T, Coghill D, Santosh P, Zuddas A, Asherson P, Buitelaar J, et al. [Long-acting medications for the treatment of hyperkinetic disorders—a systematic review and European treatment guideline. Part 1: overview and recommendations]. Z Kinder Jugendpsychiatr Psychother. 2008;36:81–94.
16. European Medicines Agency. Methylphenidate summary of product characteristics. Annex II: scientific conclusions and grounds for amendment of the summary of product characteristics and package leaflets presented by the EMEA. 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Methylphenidate_31/WC500011138.pdf. Accessed 22 Nov 2013.
17. European Medicines Agency. Methylphenidate summary of product characteristics. Annex I: list of the names, pharmaceutical forms, strengths of the medicinal products, route of administration, marketing authorisation holders in the member states (EU/EEA). 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Methylphenidate_31/WC500011138.pdf. Accessed 22 Nov 2013.
18. Janssen-Cilag Ltd. Concerta® (methylphenidate hydrochloride prolonged-release tablets) summary of product characteristics. 2013. http://www.medicines.org.uk. Accessed 29 Nov 2013.
19. Shire Inc. Elvanse® (lisdexamfetamine dimesylate capsules) summary of product characteristics. 2013. http://www.medicines.org.uk. Accessed 22 Nov 2013.
20. Medice Arzneimittel Pütter GmbH & Co. Medice receives first German authorisation for treatment of adult ADHD. http://www.medice.de/service-en/news/medice-receives-first-german-authorisation-for-treatment-of-adult-adhd. Accessed 29 Jan 2014.
21. Janssen Inc. Concerta® (methylphenidate hydrochloride) prescribing information. 2013. http://www.concerta.net/adult/prescribing-information.html. Accessed 17 Sep 2013.
22. Janssen Inc. Concerta® (methylphenidate hydrochloride) product monograph. 2012. http://www.hc-sc.gc.ca. Accessed 17 Sep 2013.
23. Novartis Inc. Ritalin® (methylphenidate hydrochloride) prescribing information. 2013. http://www.pharma.us.novartis.com/cs/www.pharma.us.novartis.com/product/pi/pdf/ritalin_ritalin-sr.pdf. Accessed 17 Sep 2013.
24. Novartis Inc. Ritalin® (methylphenidate hydrochloride) product monograph. 2013. http://www.hc-sc.gc.ca. Accessed 17 Sep 2013.
25. Eli Lilly Inc. Strattera® (atomoxetine capsules) prescribing information. 2013. http://www.strattera.com/Pages/index.aspx. Accessed 17 Sep 2013.
26. Eli Lilly Inc. Strattera® (atomoxetine capsules) product monograph. 2013. http://www.hc-sc.gc.ca. Accessed 17 Sep 2013.
27. Shire Inc. Vyvanse® (lisdexamfetamine dimesylate capsules) prescribing information. 2013. http://pi.shirecontent.com/?product=vyvanse. Accessed 17 Sep 2013.
28. Shire Inc. Vyvanse® (lisdexamfetamine dimesylate capsules) product monograph. 2013. http://www.hc-sc.gc.ca. Accessed 17 Sep 2013.
29. Faraone SV, Biederman J, Zimmerman B. An analysis of patient adherence to treatment during a 1-year, open-label study of OROS methylphenidate in children with ADHD. J Atten Disord. 2007;11:157–66.
30. Weisler RH. Review of long-acting stimulants in the treatment of attention deficit hyperactivity disorder. Expert Opin Pharmacother. 2007;8:745–58.
31. Ramos-Quiroga JA, Bosch R, Castells X, Valero S, Nogueira M, Gomez N, et al. Effect of switching drug formulations from immediate-release to extended-release OROS methylphenidate: a chart review of Spanish adults with attention-deficit hyperactivity disorder. CNS Drugs. 2008;22:603–11.
32. Swanson J, Gupta S, Lam A, Shoulson I, Lerner M, Modi N, et al. Development of a new once-a-day formulation of methylphenidate for the treatment of attention-deficit/hyperactivity disorder: proof-of-concept and proof-of-product studies. Arch Gen Psychiatry. 2003;60:204–11.
33. Wolraich ML, Doffing MA. Pharmacokinetic considerations in the treatment of attention-deficit hyperactivity disorder with methylphenidate. CNS Drugs. 2004;18:243–50.
34. Hechtman L. Effects of treatment on the overall functioning of children with ADHD. Can Child Adolesc Psychiatr Rev. 2005;14:10–5.
35. Steele M, Weiss M, Swanson J, Wang J, Prinzo RS, Binder CE. A randomized, controlled effectiveness trial of OROS-methylphenidate compared to usual care with immediate-release methylphenidate in attention deficit-hyperactivity disorder. Can J Clin Pharmacol. 2006;13:e50–62.
36. Scheffler RM, Hinshaw SP, Modrek S, Levine P. The global market for ADHD medications. Health Aff (Millwood). 2007;26:450–7.
37. Volkow ND, Wang G, Fowler JS, Logan J, Gerasimov M, Maynard L, et al. Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. J Neurosci. 2001;21:RC121.
38. Volkow ND, Fowler JS, Wang G, Ding Y, Gatley SJ. Mechanism of action of methylphenidate: insights from PET imaging studies. J Atten Disord. 2002;6(Suppl 1):S31–43.
39. Challman TD, Lipsky JJ. Methylphenidate: its pharmacology and uses. Mayo Clin Proc. 2000;75:711–21.
40. Hodgkins P, Shaw M, McCarthy S, Sallee FR. The pharmacology and clinical outcomes of amphetamines to treat ADHD: does composition matter? CNS Drugs. 2012;26:245–68.
41. Kieling C, Genro JP, Hutz MH, Rohde LA. A current update on ADHD pharmacogenomics. Pharmacogenomics. 2010;11:407–19.
42. Fallu A, Veri M, McIntyre R. ADHD and bipolar in adult patients. Presented at the 2nd International Congress on ADHD. Vienna, Austria. 2009.
43. Pliszka SR, Crismon ML, Hughes CW, Corners CK, Emslie GJ, Jensen PS, et al. The Texas Children's Medication Algorithm Project: revision of the algorithm for pharmacotherapy of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2006;45:642–57.
44. Pelham WE, Gnagy EM, Burrows-Maclean L, Williams A, Fabiano GA, Morrisey SM, et al. Once-a-day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. Pediatrics. 2001;107:E105.
45. Wolraich ML, Greenhill LL, Pelham W, Swanson J, Wilens T, Palumbo D, et al. Randomized, controlled trial of OROS methylphenidate once a day in children with attention-deficit/hyperactivity disorder. Pediatrics. 2001;108:883–92.
46. Lee SI, Hong SD, Kim SY, Kim EJ, Kim JH, Kim JH, et al. Efficacy and tolerability of OROS methylphenidate in Korean children with attention-deficit/hyperactivity disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31:210–6.
47. Zheng Y, Wang YF, Qin J, Wang LW, Zou LP, Jin XM, et al. Prospective, naturalistic study of open-label OROS methylphenidate treatment in Chinese school-aged children with attention-deficit/hyperactivity disorder. Chin Med J (Engl). 2011;124:3269–74.
48. Song DH, Choi S, Joung YS, Ha EH, Kim BN, Shin YJ, et al. Titrating optimal dose of osmotic-controlled release oral delivery (OROS)-methylphenidate and its efficacy and safety in

Korean children with ADHD: a multisite open labeled study. Psychiatry Investig. 2012;9:257–62.
49. Wilens T, McBurnett K, Stein M, Lerner M, Spencer T, Wolraich M. ADHD treatment with once-daily OROS methylphenidate: final results from a long-term open-label study. J Am Acad Child Adolesc Psychiatry. 2005;44:1015–23.
50. Wilens T, Pelham W, Stein M, Conners CK, Abikoff H, Atkins M, et al. ADHD treatment with once-daily OROS methylphenidate: interim 12-month results from a long-term open-label study. J Am Acad Child Adolesc Psychiatry. 2003;42:424–33.
51. Gerwe M, Stollhoff K, Mossakowski J, Kuehle HJ, Goertz U, Schaefer C, et al. Tolerability and effects of OROS(R) MPH (Concerta (R)) on functioning, severity of disease and quality of life in children and adolescents with ADHD: results from a prospective, non-interventional trial. Atten Defic Hyperact Disord. 2009;1:175–86.
52. Wigal SB, Wigal T, Schuck S, Brams M, Williamson D, Armstrong RB, et al. Academic, behavioral, and cognitive effects of OROS(R) methylphenidate on older children with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2011;21:121–31.
53. Blum NJ, Jawad AF, Clarke AT, Power TJ. Effect of osmotic-release oral system methylphenidate on different domains of attention and executive functioning in children with attention-deficit-hyperactivity disorder. Dev Med Child Neurol. 2011;53:843–9.
54. Murray DW, Childress A, Giblin J, Williamson D, Armstrong R, Starr HL. Effects of OROS methylphenidate on academic, behavioral, and cognitive tasks in children 9 to 12 years of age with attention-deficit/hyperactivity disorder. Clin Pediatr (Phila). 2011;50:308–20.
55. Buitelaar J, Medori R. Treating attention-deficit/hyperactivity disorder beyond symptom control alone in children and adolescents: a review of the potential benefits of long-acting stimulants. Eur Child Adolesc Psychiatry. 2010;19:325–40.
56. Coghill D, Soutullo C, d'Aubuisson C, Preuss U, Lindback T, Silverberg M, et al. Impact of attention-deficit/hyperactivity disorder on the patient and family: results from a European survey. Child Adolesc Psychiatry Ment Health. 2008;2:31.
57. Favreau A, Deseille-Turlotte G, Brault F, Giraudeau B, Krier C, Barthez MA, et al. Benefit of the extended-release methylphenidate formulations: a comparative study in childhood. Arch Pediatr. 2006;13:442–8.
58. Lopez F, Silva R, Pestreich L, Muniz R. Comparative efficacy of two once daily methylphenidate formulations (Ritalin LA and Concerta) and placebo in children with attention deficit hyperactivity disorder across the school day. Paediatr Drugs. 2003;5:545–55.
59. Silva R, Muniz R, Pestreich LK, Brams M, Childress A, Lopez FA. Efficacy of two long-acting methylphenidate formulations in children with attention- deficit/hyperactivity disorder in a laboratory classroom setting. J Child Adolesc Psychopharmacol. 2005;15:637–54.
60. Swanson JM, Wigal SB, Wigal T, Sonuga-Barke E, Greenhill LL, Biederman J, et al. A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the COMACS study). Pediatrics. 2004;113:e206–16.
61. Sonuga-Barke EJ, Swanson JM, Coghill D, DeCory HH, Hatch SJ. Efficacy of two once-daily methylphenidate formulations compared across dose levels at different times of the day: preliminary indications from a secondary analysis of the COMACS study data. BMC Psychiatry. 2004;4:28.
62. Sonuga-Barke EJ, Van LP, Swanson JM, Coghill D, Wigal S, Vandenberghe M, et al. Heterogeneity in the pharmacodynamics of two long-acting methylphenidate formulations for children with attention deficit/hyperactivity disorder. A growth mixture modelling analysis. Eur Child Adolesc Psychiatry. 2008;17:245–54.
63. Muniz R, Brams M, Mao A, McCague K, Pestreich L, Silva R. Efficacy and safety of extended-release dexmethylphenidate compared with D,L-methylphenidate and placebo in the treatment of children with attention-deficit/hyperactivity disorder: a 12-hour laboratory classroom study. J Child Adolesc Psychopharmacol. 2008;18:248–56.
64. Silva R, Muniz R, McCague K, Childress A, Brams M, Mao A. Treatment of children with attention-deficit/hyperactivity disorder: results of a randomized, multicenter, double-blind, crossover study of extended-release dexmethylphenidate and D,L-methylphenidate and placebo in a laboratory classroom setting. Psychopharmacol Bull. 2008;41:19–33.
65. Wilson HK, Cox DJ, Merkel RL, Moore M, Coghill D. Effect of extended release stimulant-based medications on neuropsychological functioning among adolescents with attention-deficit/hyperactivity disorder. Arch Clin Neuropsychol. 2006;21:797–807.
66. Cox DJ, Merkel RL, Moore M, Thorndike F, Muller C, Kovatchev B. Relative benefits of stimulant therapy with OROS methylphenidate versus mixed amphetamine salts extended release in improving the driving performance of adolescent drivers with attention-deficit/hyperactivity disorder. Pediatrics. 2006;118:e704–10.
67. Coghill D, Banaschewski T, Lecendreux M, Soutullo C, Johnson M, Zuddas A, et al. European, randomized, phase 3 study of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder. Eur Neuropsychopharmacol. 2013;23:1208–18.
68. Soutullo C, Banaschewski T, Lecendreux M, Johnson M, Zuddas A, Anderson C, et al. A post hoc comparison of the effects of lisdexamfetamine dimesylate and osmotic-release oral system methylphenidate on symptoms of attention-deficit hyperactivity disorder in children and adolescents. CNS Drugs. 2013;27:743–51.
69. Kemner JE, Starr HL, Ciccone PE, Hooper-Wood CG, Crockett RS. Outcomes of OROS methylphenidate compared with atomoxetine in children with ADHD: a multicenter, randomized prospective study. Adv Ther. 2005;22:498–512.
70. Starr HL, Kemner J. Multicenter, randomized, open-label study of OROS methylphenidate versus atomoxetine: treatment outcomes in African–American children with ADHD. J Natl Med Assoc. 2005;97:11S–6S.
71. Newcorn JH, Kratochvil CJ, Allen AJ, Casat CD, Ruff DD, Moore RJ, et al. Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute comparison and differential response. Am J Psychiatry. 2008;165:721–30.
72. Yildiz O, Sismanlar SG, Memik NC, Karakaya I, Agaoglu B. Atomoxetine and methylphenidate treatment in children with ADHD: the efficacy, tolerability and effects on executive functions. Child Psychiatry Hum Dev. 2011;42:257–69.
73. Arnold LE. Methylphenidate vs amphetamine: comparative review. J Atten Disord. 2000;3:200–11.
74. Wilens TE, McBurnett K, Bukstein O, McGough J, Greenhill L, Lerner M, et al. Multisite controlled study of OROS methylphenidate in the treatment of adolescents with attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med. 2006;160:82–90.
75. McGough JJ, McBurnett K, Bukstein O, Wilens TE, Greenhill L, Lerner M, et al. Once-daily OROS methylphenidate is safe and well tolerated in adolescents with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2006;16:351–6.

76. Newcorn JH, Stein MA, Cooper KM. Dose-response characteristics in adolescents with attention-deficit/hyperactivity disorder treated with OROS methylphenidate in a 4-week, open-label, dose-titration study. J Child Adolesc Psychopharmacol. 2010;20:187–96.
77. Na KS, Lee SI, Hong SD, Kim JH, Shim SH, Choi J, et al. Effect of osmotic-release oral system methylphenidate on learning skills in adolescents with attention-deficit/hyperactivity disorder: an open-label study. Int Clin Psychopharmacol. 2013;28:184–92.
78. Cox DJ, Merkel RL, Penberthy JK, Kovatchev B, Hankin CS. Impact of methylphenidate delivery profiles on driving performance of adolescents with attention-deficit/hyperactivity disorder: a pilot study. J Am Acad Child Adolesc Psychiatry. 2004;43:269–75.
79. Cox DJ, Merkel RL, Kovatchev B, Seward R. Effect of stimulant medication on driving performance of young adults with attention-deficit hyperactivity disorder: a preliminary double-blind placebo controlled trial. J Nerv Ment Dis. 2000;188:230–4.
80. Cox DJ, Humphrey JW, Merkel RL, Penberthy JK, Kovatchev B. Controlled-release methylphenidate improves attention during on-road driving by adolescents with attention-deficit/hyperactivity disorder. J Am Board Fam Pract. 2004;17:235–9.
81. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry. 2007;164:942–8.
82. Polanczyk G, Rohde LA. Epidemiology of attention-deficit/hyperactivity disorder across the lifespan. Curr Opin Psychiatry. 2007;20:386–92.
83. McBurnett K, Starr HL. OROS methylphenidate hydrochloride for adult patients with attention deficit/hyperactivity disorder. Expert Opin Pharmacother. 2011;12:315–24.
84. Eli Lilly Inc. Strattera® (atomoxetine capsules) summary of product characteristics. 2013. http://www.medicines.org.uk. Accessed 22 Nov 2013.
85. Biederman J, Mick E, Surman C, Doyle R, Hammerness P, Harpold T, et al. A randomized, placebo-controlled trial of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry. 2006;59:829–35.
86. Biederman J, Mick E, Spencer T, Surman C, Hammerness P, Doyle R, et al. An open-label trial of OROS methylphenidate in adults with late-onset ADHD. CNS Spectr. 2006;11:390–6.
87. Fallu A, Richard C, Prinzo R, Binder C. Does OROS-methylphenidate improve core symptoms and deficits in executive function? Results of an open-label trial in adults with attention deficit hyperactivity disorder. Curr Med Res Opin. 2006;22:2557–66.
88. Ramos-Quiroga JA, Montoya A, Kutzelnigg A, Deberdt W, Sobanski E. Attention deficit hyperactivity disorder in the European adult population: prevalence, disease awareness, and treatment guidelines. Curr Med Res Opin. 2013;29(9):1093–104.
89. Medori R, Ramos-Quiroga JA, Casas M, Kooij JJ, Niemela A, Trott GE, et al. A randomized, placebo-controlled trial of three fixed dosages of prolonged-release OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry. 2008;63:981–9.
90. Rosler M, Ginsberg Y, Arngrim T, Adamou M, Niemela A, Dejonkheere J, et al. Correlation of symptomatic improvements with functional improvements and patient-reported outcomes in adults with attention-deficit/hyperactivity disorder treated with OROS methylphenidate. World J Biol Psychiatry. 2013;14:282–90.
91. Buitelaar JK, Ramos-Quiroga JA, Casas M, Kooij JJ, Niemela A, Konofal E, et al. Safety and tolerability of flexible dosages of prolonged-release OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. Neuropsychiatr Dis Treat. 2009;5:457–66.
92. Buitelaar JK, Casas M, Philipsen A, Kooij JJ, Ramos-Quiroga JA, Dejonckheere J, et al. Functional improvement and correlations with symptomatic improvement in adults with attention deficit hyperactivity disorder receiving long-acting methylphenidate. Psychol Med. 2012;42:195–204.
93. Casas M, Rosler M, Sandra Kooij JJ, Ginsberg Y, Ramos-Quiroga JA, Heger S, et al. Efficacy and safety of prolonged-release OROS methylphenidate in adults with attention deficit/hyperactivity disorder: a 13-week, randomized, double-blind, placebo-controlled, fixed-dose study. World J Biol Psychiatry. 2013;14:268–281.
94. Adler LA, Zimmerman B, Starr HL, Silber S, Palumbo J, Orman C, et al. Efficacy and safety of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, double-blind, parallel group, dose-escalation study. J Clin Psychopharmacol. 2009;29:239–47.
95. Mattos P, Louza MR, Palmini AL, Oliveira IR, Rocha FL. A multicenter, open-label trial to evaluate the quality of life in adults with ADHD treated with long-acting methylphenidate (OROS MPH): Concerta Quality of Life (CONQoL) study. J Atten Disord. 2012;17:444–8.
96. Brod M, Johnston J, Able S, Swindle R. Validation of the adult Attention-Deficit/Hyperactivity Disorder Quality-of-Life Scale (AAQoL): a disease-specific quality-of-life measure. Qual Life Res. 2006;15:117–29.
97. Biederman J, Mick E, Surman C, Doyle R, Hammerness P, Kotarski M, et al. A randomized, 3-phase, 34-week, double-blind, long-term efficacy study of osmotic-release oral system-methylphenidate in adults with attention-deficit/hyperactivity disorder. J Clin Psychopharmacol. 2010;30:549–53.
98. Adler LA, Orman C, Starr HL, Silber S, Palumbo J, Cooper K, et al. Long-term safety of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder: an open-label, dose-titration, 1-year study. J Clin Psychopharmacol. 2011;31:108–14.
99. Chronis-Tuscano A, Seymour KE, Stein MA, Jones HA, Jiles CD, Rooney ME, et al. Efficacy of osmotic-release oral system (OROS) methylphenidate for mothers with attention-deficit/hyperactivity disorder (ADHD): preliminary report of effects on ADHD symptoms and parenting. J Clin Psychiatry. 2008;69:1938–47.
100. Food and Drug Administration. Guidance for industry: bioequivalence recommendations for specific products. 2010. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. Accessed 11 Sep 2013.
101. Health Canada. Comparative bioavailability standards: formulations used for systemic effects. 2012. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/bio/gd_standards_ld_normes-eng.php. Accessed 11 Sep 2013.
102. Food and Drug Administration. Advisory Committee for Pharmaceutical Science and Clinical Pharmacology. 2010. http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm201700.htm. Accessed 11 Sep 2013.
103. Office of the Commissioner for Federal Justice Affairs Canada. Docket T-780-08. 2010. http://reports.fja-cmf.gc.ca/eng/2010/2010fc42.html. Accessed 11 Sep 2013.
104. Teva Canada Ltd. Teva-methylphenidate ER-C (methylphenidate hydrochloride) product monograph. 2012. http://www.hc-sc.gc.ca. Accessed 11 Sep 2013.
105. Alberta College of Physicians. Novo-methylphenidate ER C requires a triplicate prescription. 2010. http://www.industrymailout.com/Industry/View.aspx?id=189199&p=c547. Accessed 11 Sep 2013.

106. Tothfalusi L, Speidl S, Endrenyi L. Exposure-response analysis reveals that clinically important toxicity difference can exist between bioequivalent carbamazepine tablets. Br J Clin Pharmacol. 2008;65:110–22.
107. Chenu F, Batten LA, Zernig G, Ladstaetter E, Hebert C, Blier P. Comparison of pharmacokinetic profiles of brand-name and generic formulations of citalopram and venlafaxine: a crossover study. J Clin Psychiatry. 2009;70:958–66.
108. Mofsen R, Balter J. Case reports of the reemergence of psychotic symptoms after conversion from brand-name clozapine to a generic formulation. Clin Ther. 2001;23:1720–31.
109. Van Ameringen M, Mancini C, Patterson B, Bennett M. Symptom relapse following switch from Celexa to generic citalopram: an anxiety disorders case series. J Psychopharmacol. 2007;21:472–6.
110. Rosenthal J, Kong B, Jacobs L, Katzman M. Did a switch to a generic antidepressant cause relapse? J Fam Pract. 2008;57:109–14.
111. van Stralen J. The clinical impact of switching ADHD patients from Concerta to a second entry product: a pediatric practice review. ADHD Atten Def Hyp Disord. 2011;3:213.
112. Fallu A, Daboux F. A randomised, double-blind cross-over, single-centre study to evaluate patient and physician reported outcomes on Concerta-OROS-methylphenidate vs the generic Novo-Methylphenidate ER-C. ADHD Atten Def Hyp Disord. 2011;3:157.
113. Greenhill L, Kollins S, Abikoff H, McCracken J, Riddle M, Swanson J, et al. Efficacy and safety of immediate-release methylphenidate treatment for preschoolers with ADHD. J Am Acad Child Adolesc Psychiatry. 2006;45:1284–93.
114. Swanson JM, Kraemer HC, Hinshaw SP, Arnold LE, Conners CK, Abikoff HB, et al. Clinical relevance of the primary findings of the MTA: success rates based on severity of ADHD and ODD symptoms at the end of treatment. J Am Acad Child Adolesc Psychiatry. 2001;40:168–79.
115. Chou WJ, Chen SJ, Chen YS, Liang HY, Lin CC, Tang CS, et al. Remission in children and adolescents diagnosed with attention-deficit/hyperactivity disorder via an effective and tolerable titration scheme for osmotic release oral system methylphenidate. J Child Adolesc Psychopharmacol. 2012;22:215–25.
116. Gau SS, Chen SJ, Chou WJ, Cheng H, Tang CS, Chang HL, et al. National survey of adherence, efficacy, and side effects of methylphenidate in children with attention-deficit/hyperactivity disorder in Taiwan. J Clin Psychiatry. 2008;69:131–40.
117. Dickson RA, Maki E, Gibbins C, Gutkin SW, Turgay A, Weiss MD. Time courses of improvement and symptom remission in children treated with atomoxetine for attention-deficit/hyperactivity disorder: analysis of Canadian open-label studies. Child Adolesc Psychiatry Ment Health. 2011;5:14.
118. Kelsey DK, Sumner CR, Casat CD, Coury DL, Quintana H, Saylor KE, et al. Once-daily atomoxetine treatment for children with attention-deficit/hyperactivity disorder, including an assessment of evening and morning behavior: a double-blind, placebo-controlled trial. Pediatrics. 2004;114:e1–8.
119. Michelson D, Allen AJ, Busner J, Casat C, Dunn D, Kratochvil C, et al. Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: a randomized, placebo-controlled study. Am J Psychiatry. 2002;159:1896–901.
120. Ramos-Quiroga JA, Casas M. Achieving remission as a routine goal of pharmacotherapy in attention-deficit hyperactivity disorder. CNS Drugs. 2011;25:17–36.
121. Steele M, Jensen PS, Quinn DM. Remission versus response as the goal of therapy in ADHD: a new standard for the field? Clin Ther. 2006;28:1892–908.
122. Remschmidt H, Hoare P, Ettrich C, Rothenberger A, Santosh P, Schmidt M, et al. Symptom control in children and adolescents with attention-deficit/hyperactivity disorder on switching from immediate-release MPH to OROS MPH: results of a 3-week open-label study. Eur Child Adolesc Psychiatry. 2005;14:297–304.
123. Hoare P, Remschmidt H, Medori R, Ettrich C, Rothenberger A, Santosh P, et al. 12-month efficacy and safety of OROS MPH in children and adolescents with attention-deficit/hyperactivity disorder switched from MPH. Eur Child Adolesc Psychiatry. 2005;14:305–9.
124. Kim Y, Shin MS, Kim JW, Yoo HJ, Cho SC, Kim BN. Neurocognitive effects of switching from methylphenidate-IR to OROS-methylphenidate in children with ADHD. Hum Psychopharmacol. 2009;24:95–102.
125. Kordon A, Stollhoff K, Niederkirchner K, Mattejat F, Rettig K, Schauble B. Exploring the impact of once-daily OROS(R) methylphenidate (MPH) on symptoms and quality of life in children and adolescents with ADHD transitioning from immediate-release MPH. Postgrad Med. 2011;123:27–38.
126. Spencer TJ, Mick E, Surman CB, Hammerness P, Doyle R, Aleardi M, et al. A randomized, single-blind, substitution study of OROS methylphenidate (Concerta) in ADHD adults receiving immediate release methylphenidate. J Atten Disord. 2011;15:286–94.
127. Wolff C, Alfred A, Lindermuller A, Rettig K, Mattejat F, Gerwe M, et al. Effect of transitioning from extended-release methylphenidate onto osmotic, controlled-release methylphenidate in children/adolescents with ADHD: results of a 3-month non-interventional study. Curr Med Res Opin. 2011;27(Suppl 2):35–44.
128. Niederkirchner K, Slawik L, Wermelskirchen D, Rettig K, Schauble B. Transitioning to OROS((R)) methylphenidate from atomoxetine is effective in children and adolescents with ADHD. Expert Rev Neurother. 2011;11:499–508.
129. Adler LA, Reingold LS, Morrill MS, Wilens TE. Combination pharmacotherapy for adult ADHD. Curr Psychiatry Rep. 2006;8:409–15.
130. Pohl GM, Van Brunt DL, Ye W, Stoops WW, Johnston JA. A retrospective claims analysis of combination therapy in the treatment of adult attention-deficit/hyperactivity disorder (ADHD). BMC Health Serv Res. 2009;9:95.
131. Brown TE. Atomoxetine and stimulants in combination for treatment of attention deficit hyperactivity disorder: four case reports. J Child Adolesc Psychopharmacol. 2004;14:129–36.
132. Hammerness P, Georgiopoulos A, Doyle RL, Utzinger L, Schillinger M, Martelon M, et al. An open study of adjunct OROS-methylphenidate in children who are atomoxetine partial responders: II. Tolerability and pharmacokinetics. J Child Adolesc Psychopharmacol. 2009;19:493–9.
133. Wilens TE, Hammerness P, Utzinger L, Schillinger M, Georgiopoulous A, Doyle RL, et al. An open study of adjunct OROS-methylphenidate in children and adolescents who are atomoxetine partial responders: I. Effectiveness. J Child Adolesc Psychopharmacol. 2009;19:485–92.
134. Gau SS, Ni HC, Shang CY, Soong WT, Wu YY, Lin LY, et al. Psychiatric comorbidity among children and adolescents with and without persistent attention-deficit hyperactivity disorder. Aust N Z J Psychiatry. 2010;44:135–43.
135. Ryan-Krause P. Attention deficit hyperactivity disorder: part I. J Pediatr Health Care. 2010;24:194–8.
136. Spencer TJ, Biederman J, Mick E. Attention-deficit/hyperactivity disorder: diagnosis, lifespan, comorbidities, and neurobiology. Ambul Pediatr. 2007;7:73–81.
137. Jarrett MA, Wolff JC, Davis TE, Cowart MJ, Ollendick TH. Characteristics of children with ADHD and comorbid anxiety. J Atten Disord. 2012. doi:10.1177/1087054712452914.

138. Klassen LJ, Katzman MA, Chokka P. Adult ADHD and its comorbidities, with a focus on bipolar disorder. J Affect Disord. 2010;124:1–8.
139. Greenhill LL, Swanson JM, Vitiello B, Davies M, Clevenger W, Wu M, et al. Impairment and deportment responses to different methylphenidate doses in children with ADHD: the MTA titration trial. J Am Acad Child Adolesc Psychiatry. 2001;40: 180–7.
140. Ter-Stepanian M, Grizenko N, Zappitelli M, Joober R. Clinical response to methylphenidate in children diagnosed with attention-deficit hyperactivity disorder and comorbid psychiatric disorders. Can J Psychiatry. 2010;55:305–12.
141. Connor DF, Glatt SJ, Lopez ID, Jackson D, Melloni RH Jr. Psychopharmacology and aggression. I: a meta-analysis of stimulant effects on overt/covert aggression-related behaviors in ADHD. J Am Acad Child Adolesc Psychiatry. 2002;41:253–61.
142. MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD. Arch Gen Psychiatry. 1999;56:1073–86.
143. Serra-Pinheiro MA, Mattos P, Souza I, Pastura G, Gomes F. The effect of methylphenidate on oppositional defiant disorder comorbid with attention deficit/hyperactivity disorder. Arq Neuropsiquiatr. 2004;62:399–402.
144. Kronenberger WG, Giauque AL, Lafata DE, Bohnstedt BN, Maxey LE, Dunn DW. Quetiapine addition in methylphenidate treatment-resistant adolescents with comorbid ADHD, conduct/oppositional-defiant disorder, and aggression: a prospective, open-label study. J Child Adolesc Psychopharmacol. 2007;17: 334–47.
145. Reimherr FW, Williams ED, Strong RE, Mestas R, Soni P, Marchant BK. A double-blind, placebo-controlled, crossover study of osmotic release oral system methylphenidate in adults with ADHD with assessment of oppositional and emotional dimensions of the disorder. J Clin Psychiatry. 2007;68:93–101.
146. Marchant BK, Reimherr FW, Halls C, Williams ED, Strong RE. OROS methylphenidate in the treatment of adults with ADHD: a 6-month, open-label, follow-up study. Ann Clin Psychiatry. 2010;22:196–204.
147. Mariani JJ, Levin FR. Treatment strategies for co-occurring ADHD and substance use disorders. Am J Addict. 2007;16(Suppl 1):45–54.
148. Klassen LJ, Bilkey TS, Katzman MA, Chokka P. Comorbid attention deficit/hyperactivity disorder and substance use disorder: treatment considerations. Curr Drug Abuse Rev. 2012;5:190–8.
149. Castaneda R, Sussman N, Levy R, Trujillo M. A treatment algorithm for attention deficit hyperactivity disorder in cocaine-dependent adults: a one-year private practice study with long-acting stimulants, fluoxetine, and bupropion. Subst Abus. 1999;20:59–71.
150. Levin FR, Evans SM, Brooks DJ, Garawi F. Treatment of cocaine dependent treatment seekers with adult ADHD: double-blind comparison of methylphenidate and placebo. Drug Alcohol Depend. 2007;87:20–9.
151. Somoza EC, Winhusen TM, Bridge TP, Rotrosen JP, Vanderburg DG, Harrer JM, et al. An open-label pilot study of methylphenidate in the treatment of cocaine dependent patients with adult attention deficit/hyperactivity disorder. J Addict Dis. 2004;23:77–92.
152. Levin FR, Evans SM, Brooks DJ, Kalbag AS, Garawi F, Nunes EV. Treatment of methadone-maintained patients with adult ADHD: double-blind comparison of methylphenidate, bupropion and placebo. Drug Alcohol Depend. 2006;81:137–48.
153. Schubiner H, Saules KK, Arfken CL, Johanson CE, Schuster CR, Lockhart N, et al. Double-blind placebo-controlled trial of methylphenidate in the treatment of adult ADHD patients with comorbid cocaine dependence. Exp Clin Psychopharmacol. 2002;10:286–94.
154. Riggs PD, Winhusen T, Davies RD, Leimberger JD, Mikulich-Gilbertson S, Klein C, et al. Randomized controlled trial of osmotic-release methylphenidate with cognitive-behavioral therapy in adolescents with attention-deficit/hyperactivity disorder and substance use disorders. J Am Acad Child Adolesc Psychiatry. 2011;50:903–14.
155. Biederman J, Mick E, Spencer T, Surman C, Faraone SV. Is response to OROS-methylphenidate treatment moderated by treatment with antidepressants or psychiatric comorbidity? A secondary analysis from a large randomized double blind study of adults with ADHD. CNS Neurosci Ther. 2012;18:126–32.
156. Gadow KD, Nolan EE, Sverd J, Sprafkin J, Schwartz J. Anxiety and depression symptoms and response to methylphenidate in children with attention-deficit hyperactivity disorder and tic disorder. J Clin Psychopharmacol. 2002;22:267–74.
157. Kurlan R. Treatment of ADHD in children with tics: a randomized controlled trial. Neurology. 2002;58:527–36.
158. Steeves TD, Fox SH. Neurobiological basis of serotonin-dopamine antagonists in the treatment of Gilles de la Tourette syndrome. Prog Brain Res. 2008;172:495–513.
159. Golden GS. Gilles de la Tourette's syndrome following methylphenidate administration. Dev Med Child Neurol. 1974;16: 76–8.
160. Golden GS. The effect of central nervous system stimulants on Tourette syndrome. Ann Neurol. 1977;2:69–70.
161. Pollack MA, Cohen NL, Friedhoff AJ. Gilles de la Tourette's syndrome. Familial occurrence and precipitation by methylphenidate therapy. Arch Neurol. 1977;34:630–2.
162. Weiss G, Minde K, Douglas V, Werry J, Sykes D. Comparison of the effects of chlorpromazine, dextroamphetamine and methylphenidate on the behaviour and intellectual functioning of hyperactive children. Can Med Assoc J. 1971;104:20–5.
163. Gadow KD, Sverd J, Nolan EE, Sprafkin J, Schneider J. Immediate-release methylphenidate for ADHD in children with comorbid chronic multiple tic disorder. J Am Acad Child Adolesc Psychiatry. 2007;46:840–8.
164. Palumbo D, Spencer T, Lynch J, Co-Chien H, Faraone SV. Emergence of tics in children with ADHD: impact of once-daily OROS methylphenidate therapy. J Child Adolesc Psychopharmacol. 2004;14:185–94.
165. Hodgkins P, Shaw M, Coghill D, Hechtman L. Amfetamine and methylphenidate medications for attention-deficit/hyperactivity disorder: complementary treatment options. Eur Child Adolesc Psychiatry. 2012;21:477–92.
166. Engert V, Pruessner JC. Dopaminergic and noradrenergic contributions to functionality in ADHD: the role of methylphenidate. Curr Neuropharmacol. 2008;6:322–8.
167. Volkow ND, Wang GJ, Fowler JS, Learned-Coughlin S, Yang J, Logan J, et al. The slow and long-lasting blockade of dopamine transporters in human brain induced by the new antidepressant drug radafaxine predict poor reinforcing effects. Biol Psychiatry. 2005;57:640–6.
168. Klein-Schwartz W. Abuse and toxicity of methylphenidate. Curr Opin Pediatr. 2002;14:219–23.
169. Stevens JR, George RA, Fusillo S, Stern TA, Wilens TE. Plasma methylphenidate concentrations in youths treated with high-dose osmotic release oral system formulation. J Child Adolesc Psychopharmacol. 2010;20:49–54.