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Dexmethylphenidate Extended Release

In Attention-Deficit Hyperactivity Disorder

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Contents

Abstract

▲ Dexmethylphenidate extended release (XR) is an orally administered, bimodal release, capsule formulation of the active *d*-enantiomer of methylphenidate (MPH), which inhibits dopamine and norepinephrine (noradrenaline) reuptake to increase their concentration in the extraneuronal space.

▲ A single dose of dexmethylphenidate XR mimics the pharmacokinetic profile of two doses of dexmethylphenidate immediate-release formulation administered 4 hours apart, albeit with less fluctuation in plasma concentration.

▲ Once-daily dexmethylphenidate XR was more effective than placebo in reducing attention-deficit hyperactivity disorder (ADHD) symptom scores in children, adolescents and adults with ADHD in four randomised, double-blind, placebo-controlled trials of up to 7 weeks' duration.

▲ In crossover trials in children (aged 6–12 years), dexmethylphenidate XR 20 mg/day reduced mean ADHD symptom scores 1 hour after administration (by 43% in one trial) and was significantly better than placebo for up to 12 hours.

▲ Dexmethylphenidate XR 5–30 mg/day reduced mean ADHD symptom scores by 49%, while scores declined by 16% with placebo in a 7-week trial in children and adolescents (aged 6–17 years).

▲ Dexmethylphenidate XR 20, 30 or 40 mg/day reduced ADHD symptom scores by 36–46% versus a 21% reduction with placebo in a 5-week trial in adults (aged 18–60 years).

▲ Dexmethylphenidate XR was generally well tolerated in children, adolescents and adults with ADHD, with an adverse-event profile typical of MPH.

Features and properties of dexmethylphenidate extended release (XR) [Focalin™ XR]	
Indication	
Treatment of attention-deficit hyperactivity disorder in patients aged ≥6 years	
Mechanism of action	
Inhibition of presynaptic dopamine and norepinephrine (noradrenaline) reuptake	
Dosage and administration	
Initial dose	5–10mg
Route of administration/formulation	Oral capsule
Frequency of administration	Once daily
Weekly increments as required	5–10mg; maximum dosage 20 mg/day
Pharmacokinetic profile of oral dexmethylphenidate XR 20mg in 24 healthy adults	
First and second peak plasma concentrations (ng/mL)	≈13, ≈13
Time to first and second peak plasma concentrations (h)	≈1.5, ≈6.5
Mean clearance (L/kg/h)	0.4
Mean terminal elimination half-life (h)	3
Volume of distribution (L/kg)	2.65
Adverse events	
Most common (>5%) and incidence ≥2-fold that of placebo	Decreased appetite, headache, dry mouth, anxiety and dyspepsia

In the US, attention-deficit hyperactivity disorder (ADHD), characterised by symptoms of inattention, hyperactivity and impulsivity, has been diagnosed in 4–12% of children aged 6–12 years.[1] The persistence of the condition into adulthood is estimated to have a prevalence of 1–6%.[2] Of the working population in the US, 4.2% of those aged 18–44 years are affected and economic losses due to lost work performance are estimated at $US19.6 billion annually.[3]

The medications used most commonly in the treatment of ADHD are stimulants such as methylphenidate (MPH) and dexamfetamine.[4]

MPH is composed of equal proportions of its *d*- and *l*-enantiomers; however, the pharmacological efficacy of MPH is ascribed entirely to the *d*-enantiomer, dexmethylphenidate (see section 1),[5] which has been in clinical use for the treatment of ADHD for several years.[6] The half-life of immediate-release (IR) dexmethylphenidate is only 2–3 hours (section 2), so multiple daily dosing is required to provide adequate drug coverage. For convenience, compliance and to avoid drug diversion problems, a formulation requiring administration only once daily is desirable.[7]

The focus of this article is an extended-release (XR) capsule formulation of dexmethylphenidate (Focalin™ XR),[1] approved in the US for the treatment of ADHD in patients aged ≥6 years.[8]

1. Pharmacodynamic Profile

The pharmacodynamics of the *d*- and *l*-enantiomers of MPH and of a racemic mixture of the two have been examined in an animal model,[9] a randomised, double-blind, crossover study in nine children (mean age 11.1 years) with ADHD, [5] and a randomised, double-blind, placebo-controlled 4-week trial in 132 children (mean age 9.8 years) with ADHD.[10] Data from the manufacturer's prescribing information[8] and further relevant data concerning the pharmacodynamics of racemic MPH[11,12] are also presented.

- While the mechanism of action of dexmethylphenidate is uncertain, it appears to act via inhibition of presynaptic dopamine and norepinephrine (noradrenaline) reuptake, thereby increasing the concentration of these monoamine neurotransmitters in the extraneuronal space.[8,9]

- The pharmacodynamic activity of MPH is attributed to the *d*-enantiomer.[5,9] In an *in vivo* study in rats, the *d*-enantiomer and racemic MPH, but not the *l*-enantiomer, altered functional observational battery evaluation and rota-rod test scores indicative of psychostimulation.[9]

- In the crossover study in children,[5] mean scanning reaction time test scores (a measure of continuous performance) in seven children were significantly higher ($p < 0.05$) with racemic MPH 10mg or the *d*-enantiomer 5mg than with the *l*-enantiomer 5mg or placebo. Differences between the *d*-enantiomer and racemic MPH were not significant,[5] although it has been suggested that the *d*-enantiomer may have a longer duration of action than racemic MPH and may permit the use of less than equimolar doses of the *d*-enantiomer.[13]

- In the placebo-controlled 4-week trial,[10] 39 or 50% reductions in teacher-assessed Swanson, Nolan and Pelham (SNAP) rating scale scores were observed after twice-daily dosing with either the *d*-enantiomer ($n = 44$) or racemic MPH ($n = 46$) that were significantly ($p < 0.005$) greater than after placebo (13%; $n = 42$). Parent-assessed SNAP ratings were also reduced from baseline (40%; $p < 0.0003$) in recipients of the *d*-enantiomer 5.5–6.5 hours after the second dose of medication, but not in those receiving racemic MPH (24%), providing some support for a longer duration of action of the *d*-enantiomer.[10]

- Increases in heart rate and blood pressure (BP) have been associated with MPH administration.[11,12] Similarly, small increases in heart rate and BP have been observed in dexmethylphenidate XR recipients (section 4).[8,14-16] Although the clinical significance of these effects is unknown, BP should be monitored

1 The use of trade names is for product identification purposes only and does not imply endorsement.

at appropriate intervals, especially in patients with hypertension.

● While reductions in growth velocity and weight during adolescence have been observed in some studies of MPH, a causal relationship has not been established, and post-adolescent height and weight do not appear to be reduced.[12] It has been suggested that temporary growth suppression may be a pathological manifestation of ADHD;[17] however, a recent analysis suggests that medication use (mostly MPH[18]) induces significant height suppression.[19] Data concerning the effect of long-term dexmethylphenidate XR therapy are not available.[8]

2. Pharmacokinetic Profile

Most data on the dexmethylphenidate XR formulation in this section were obtained from the manufacturer's prescribing information.[8] Relevant data on the dexmethylphenidate IR formulation and racemic MPH are also reported.[8] No data are available in patients with renal or hepatic impairment, or in children or adolescents aged <18 years.

● Oral dexmethylphenidate XR has a bimodal release profile produced by the use of a capsule containing half the dose as immediate-release beads and half as enteric-coated, delayed-release beads.[8]

● In healthy adults, the initial rate of absorption of dexmethylphenidate XR 20mg (n = 24) was similar to that of two doses of dexmethylphenidate IR 10mg given 4 hours apart (n = 25), with a first mean peak plasma concentration (C_{max1}) of ≈13 ng/mL (estimated from a graph) reached in ≈1.5 hours (t_{max1}; range 1–4h).[8]

● The second mean peak plasma concentration (C_{max2}), which was also ≈13 ng/mL (estimated from a graph), was achieved with dexmethylphenidate XR at ≈6.5 hours (t_{max2}; range 4.5–7h).[8] However, C_{max2} and the peak and trough fluctuations in plasma drug concentration were numerically lower, and the interpeak minimum drug concentration was numerically higher, with a single dose of dexmethylphenidate XR than with two doses of dexmethylphenidate IR (statistical analysis not reported). The area under the plasma concentration-time curve was similar with both formulations.[8]

● The effect of food on dexmethylphenidate XR absorption has not been investigated; however, a high-fat breakfast lengthened the lag time of absorption of a similar XR formulation of racemic MPH, and produced variable delays in t_{max1}, t_{max2} and the time to the interpeak minimum concentration.[8] MPH C_{max1} and the extent of absorption were unchanged after food relative to the fasting state, whereas C_{max2} was ≈25% lower.

● The plasma protein binding of dexmethylphenidate is unknown, but racemic MPH is 12–15% plasma protein bound.[8] Dexmethylphenidate has a volume of distribution of 2.65 L/kg.

● Dexmethylphenidate is metabolised primarily by de-esterification to a primary metabolite (*d*-α-phenyl-piperidine acetic acid; *d*-ritalinic acid) with negligible pharmacological activity.[8] No interconversion between *d*- and *l*-enantiomers has been observed *in vivo*. *In vitro*, dexmethylphenidate did not inhibit cytochrome P450 isoenzymes.[8]

● Intravenous dexmethylphenidate had a mean clearance of 0.4 L/kg/h (0.56 L/min), and a mean terminal elimination half-life ($t_{1/2\beta}$) of ≈3 hours in healthy adults, and 2–3 hours in children.[8]

● In humans, ≈90% of a dose of radiolabelled racemic MPH was recovered in urine, of which ≈80% comprised ritalinic acid, and 0.5% was unchanged parent compound.[8] Owing to first-pass metabolism, the mean absolute bioavailability of oral dexmethylphenidate is 22–25%.[8]

● In adults, C_{max1} after administration of dexmethylphenidate XR was 45% higher in women than in men.[8]

● In 15 healthy children (aged 10–12 years) and three children with ADHD aged (7–9 years), the t_{max1} of racemic MPH XR was similar, but t_{max2} was delayed, compared with adults. Differences in exposure between children and adults at the same dose (≈2-fold higher concentrations in children) were attributed to differences in body size.[8]

3. Therapeutic Efficacy

The clinical efficacy of once-daily oral dexmethylphenidate XR has been examined in patients who met the Diagnostic and Statistical Manual

of Mental Disorders, 4th edition (DSM-IV) criteria for ADHD in two randomised, double-blind, crossover, placebo-controlled trials in 54[20] and 68[14] children (aged 6–12 years), and in two randomised, double-blind, parallel-group, placebo-controlled, multicentre 5-[15,16] or 7-week[21,22] trials in 221 adults (aged 18–60 years)[15] and in 103 children and adolescents (aged 6–17 years).[21] Data were obtained from abstracts and posters.[14-16,20-22]

In the crossover studies,[14,20] dexmethylphenidate XR 20 mg/day (n = 27[20] or 34[14]) or placebo (n = 27[20] or 34[14]) was administered for 5[20] or 6[14] days, followed in one trial by a 1-day washout period,[20] with evaluations conducted on day 7.[14,20] Participants were children (38[20] or 45[14] male, 16[20] or 23[14] female) with ADHD (subtypes: inattentive 9%[20] or 18%[14]; hyperactive/impulsive 0%;[14,20] combined 91%[20] or 82%[14]), previously stabilised on MPH 20–40 mg/day[14,20] or dexmethylphenidate IR 20 mg/day.[14] Evaluations were conducted on day 7 in a laboratory classroom at several timepoints up to 12 hours after administration of oral dexmethylphenidate XR 20mg or placebo. Participants then crossed over to the alternative protocol.[14,20]

In the 7-week study,[21] children and adolescents (66 male; 37 female) with ADHD (subtypes: inattentive 21%; hyperactive/impulsive 2%; combined 77%) received placebo (n = 50) or dexmethylphenidate XR 5–30 mg/day (n = 53) titrated to optimal levels over the first 5 weeks of the trial and maintained for the final 2 weeks.

In the 5-week trial,[16] adults (127 male, 94 female) with ADHD (subtypes: inattentive 27%; hyperactive/impulsive 3%; combined 70%) received placebo (n = 53) or dexmethylphenidate XR 20 (n = 58), 30 (n = 55) or 40 mg/day (n = 55) titrated in increments of 10 mg/week from an initial dosage of 10 mg/day to the randomly assigned fixed dosage and then maintained for a minimum of 2 weeks. After completing the 5-week trial,[16] 170 adults entered a nonblind, flexible-dose, 6-month extension phase in which they all received dexmethylphenidate XR.[15]

The primary endpoint in the crossover trials,[14,20] was the SKAMP (Swanson, Kotkin, Agler, M-Flynn and Pelham)-Combined score 1 hour after administration[20] or at 1, 3, 4, 5, 7, 9, 10, 11 and 12 hours,[14] with the number of mathematical problems attempted and answered correctly, SKAMP-Attention and -Deportment subscores and the SKAMP-Combined score at other timepoints as secondary endpoints.

The primary efficacy endpoint in the 7-week trial,[21,22] was the Conners' ADHD/DSM-IV Scale™ (CADS) for teachers (CADS-T) score assessed on an intent-to-treat last-observation-carried-forward basis, with secondary endpoints including the CADS for parents (CADS-P) score, the Physical and Psychosocial component scores of the Child Health Questionnaire (CHQ) Parent Form 50 and the Clinical Global Impressions Scale for Improvement (CGI-I) score. Primary efficacy in the 5-week trial,[16] was evaluated using investigator-administered, DSM-IV-based, ADHD Rating Scale (RS) total scores (assessed on an observed case basis[15]), with the proportion of patients with 'very much improved' or 'much improved' CGI-I scores and the proportion of patients with an improvement of ≥30% in ADHD RS total score as secondary variables.[15] Lower scores on all these scales represented an improvement.

- Overall, once-daily dexmethylphenidate XR was significantly more effective than placebo in reducing ADHD symptom scores in children,[14,20] adolescents[22] and adults.[16]

- In crossover studies in children (mean age ≈9.5 years) with ADHD,[14,20] dexmethylphenidate XR 20 mg/day was significantly ($p < 0.001$) more effective than placebo, reducing the mean SKAMP-Combined score at 1 hour (primary endpoint) by 43% from baseline (change in SKAMP-Combined score −10) versus a 9% rise with placebo (change in SKAMP-Combined score +0.9) in one trial (figure 1).[20] In the other trial, the reduction in SKAMP-Combined score was significantly ($p < 0.001$) greater in dexmethylphenidate XR than in placebo recipients at all timepoints up to 12 hours after

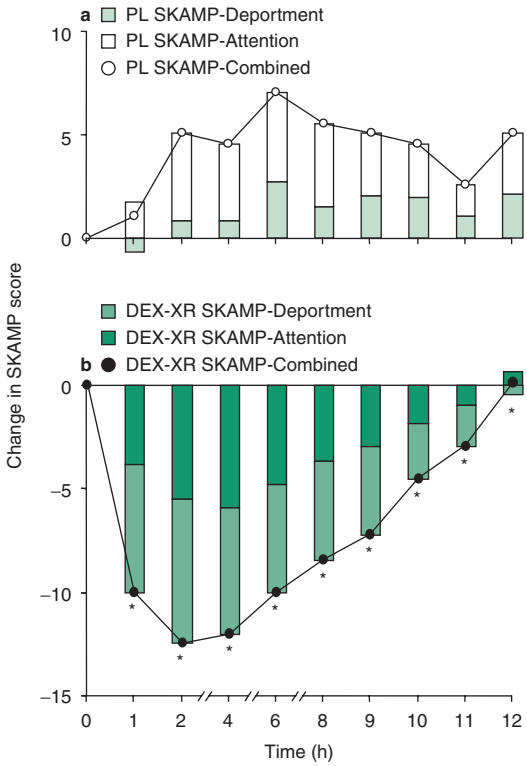

Fig. 1. Efficacy of dexmethylphenidate extended release (DEX-XR) in 54 children (aged 6–12 years) with attention-deficit hyperactivity disorder.[20] Adjusted least squares mean change from baseline in SKAMP (Swanson, Kotkin, Agler, M-Flynn and Pelham)-Combined score and SKAMP-Attention and -Deportment subscores at each timepoint up to 12 hours after oral administration of (**a**) placebo (PL) or (**b**) DEX-XR 20mg in a randomised, double-blind, crossover trial (data estimated from a graph). Data were collected on day 7, after 5 days of once-daily treatment and a one-day washout period. * $p \leq 0.001$ for SKAMP-Combined score vs PL.

administration, with an effect size of 1.49 after 12 hours.[14]

- In the 7-week study in children and adolescents (mean age 10 years) with ADHD,[21] the adjusted mean change in CADS-T score was greater in dexmethylphenidate XR (−16.3) than placebo (−5.7; $p < 0.001$) recipients (adjusted for treatment group, centre and baseline score [33.4 and 35.2]).[21]

- In the 5-week trial in adults (mean age ≈39 years) with ADHD,[16] all three dosages of dexmethylphenidate XR were more effective than placebo, reducing mean ADHD RS total scores by 36–46% versus 21% with placebo (figure 2). Mean scores were reduced by 13.7, 13.4 and 16.9 for dexmethylphenidate XR dosages of 20, 30 and 40 mg/day, respectively, from baseline values of 36.9, 36.9 and 36.7, versus a mean reduction with placebo of 7.9 from a baseline score of 37.5; no dose-dependent differences in efficacy were reported.[16]

- Secondary outcomes were also significantly in favour of dexmethylphenidate XR compared with placebo.[14,16,20-22] In both crossover trials in children,[14,20] significant ($p \leq 0.013$ vs placebo) improvements were observed at each timepoint up to 12 hours after administration of dexmethylphenidate XR in SKAMP-Combined score, SKAMP-Attention and -Deportment subscores (figure 1), and the number of mathematical problems attempted and answered correctly.

- In the 7-week trial,[21] the mean adjusted change of CADS-P score was −17.6 versus −6.5 ($p < 0.001$) from baseline values of 40.1 and 38.9 for dexmethylphenidate XR and placebo recipients. Among dexmethylphenidate XR recipients, CADS-T and CADS-P score improved from baseline by ≈20% and ≈19% in treatment-naive patients (n = 33), and by ≈9% and ≈14% in previously treated patients (n = 20) [data estimated from a graph, statistical analyses not reported].[22] The pro-

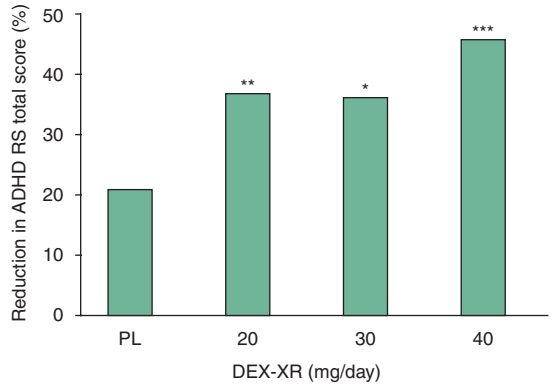

Fig. 2. Efficacy of dexmethylphenidate extended release (DEX-XR) in adults with attention-deficit hyperactivity disorder (ADHD).[16] Reduction from baseline in mean ADHD Rating Scale (RS) total scores in adults receiving placebo (PL) [n = 53] or DEX-XR 20 (n = 58), 30 (n = 55) or 40 mg/day (n = 55) for 5 weeks in a randomised, double-blind, multicentre trial. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs PL.

portion of patients rated as 'very much improved' or 'much improved' on the CGI-I score was greater with dexmethylphenidate XR than with placebo (67.3% vs 13.3%; $p < 0.001$). The improvement in the median CHQ Psychosocial component score was greater in dexmethylphenidate XR than placebo recipients (11.2% vs 2.5%; $p < 0.001$), whereas the CHQ Physical component score did not differ significantly between groups.[21,22]

- In adults treated for 5 weeks, the proportion of patients with ≥30% improvement in ADHD RS total score at the final visit was 34% with placebo versus 58% ($p = 0.017$), 54% ($p = 0.054$) and 61% ($p = 0.007$) with dexmethylphenidate XR 20, 30 or 40 mg/day, respectively.[16]
- In adults completing a nonblind, 6-month, extension phase of the 5-week trial,[15] those who switched from placebo to dexmethylphenidate XR (n = 20) improved their ADHD RS total score from the end of the double-blind phase to the final nonblind assessment by 41% (mean change −10.2), while those who continued dexmethylphenidate XR treatment (n = 82) improved by 44% (mean change −8.4). The CGI-I score was 'very much improved' or 'much improved' in 95% of patients in each group.[15]

4. Tolerability

- Dexmethylphenidate XR was generally well tolerated in children, adolescents and adults with ADHD,[8,14,16,20,22] with an adverse event profile consistent with those of MPH and other psychostimulants.[23] In a combined observational analysis of clinical trials data,[8] the most common adverse events in patients receiving dexmethylphenidate XR were decreased appetite, headache, dry mouth, anxiety and dyspepsia (figure 3).
- Anorexia was reported in four children receiving dexmethylphenidate XR but no placebo recipients in one crossover study,[20] and in two dexmethylphenidate XR recipients and one placebo recipient in the 7-week trial in children and adolescents.[22] A clinically notable (≥7%) decline in weight was observed in 11.3% of children dexmethylphenidate XR recipients but no placebo recipients.[22] Mean weight declined by 0.5kg in dexmethylphenidate XR recipients while it rose by 0.4kg in placebo recipients (statistical analysis not reported).

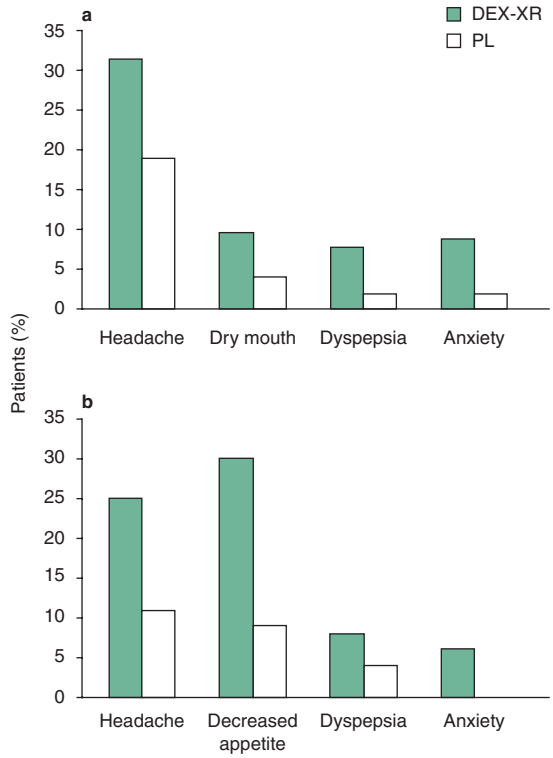

Fig. 3. Tolerability of dexmethylphenidate extended release (DEX-XR) in patients with attention-deficit hyperactivity disorder. Incidence of common (>5% in any trial) adverse events with an incidence ≥2-fold that of placebo (PL) regardless of causality in (**a**) adults receiving DEX-XR 20–40 mg/day (n = 165) or PL (n = 53) and (**b**) children and adolescents receiving DEX-XR 5–30 mg/day (n = 53) or PL (n = 47). Data from a pooled analysis of clinical trials.[8]

- In the second crossover trial,[14] the overall incidence of adverse events was identical in dexmethylphenidate XR and placebo recipients (16.2%), and the only adverse events to affect more than one patient (gastroenteritis, upper respiratory tract infection and allergic rhinitis) were more common in placebo than dexmethylphenidate XR recipients. Modest increases in systolic BP (SBP) and diastolic BP (DBP) and heart rate were similar in dexmethylphenidate XR and placebo recipients.[14]
- In the 5-week trial in adults,[16] 3.6% of dexmethylphenidate XR and 1.9% of placebo recipi-

ents experienced a clinically notable (≥7%) decline in weight.[15] Mean weight declined by 1.4kg in dexmethylphenidate XR recipients and 0.1kg in placebo recipients (statistical analysis not reported).

- In the 7-week trial in children and adolescents,[22] one dexmethylphenidate XR and one placebo recipient had a 'clinically notable' (not defined) increase in SBP and one placebo recipient had a 'clinically notable' increase in DBP. One dexmethylphenidate XR and six placebo recipients had a 'clinically notable' decrease in heart rate.[22]
- In adults,[16] mean changes in sitting SBP and DBP (−1.7 to +1.0mm Hg) did not differ significantly between groups; however, mean sitting heart rate rose in dexmethylphenidate XR recipients and declined in placebo recipients (+4.4 vs −1.4 beats/min; p = 0.0007).[15]
- Similar numbers of adult patients in the placebo and dexmethylphenidate XR 20, 30 and 40 mg/day treatment groups (4, 6, 7 and 5 patients, respectively) withdrew from the 5-week trial because of adverse events.[16] Only one serious or severe adverse event, not considered related to study medication,[14] was reported in trials in children and adolescents.[14,20,21]
- In the nonblind, 6-month extension phase[15] of the 5-week trial,[16] the most frequent adverse events were headache, insomnia and decreased appetite, and most adverse events were of mild to moderate severity. Of the 170 patients who commenced the extension phase, 14.7% withdrew because of adverse events; a high potassium level (>5 mmol/L) occurred in 3.5% of patients. By the end of the extension phase, mean weight loss was 1.8kg and 19.4% of patients had experienced weight loss of ≥7%.[15]

5. Dosage and Administration

Oral dexmethylphenidate XR is administered once daily in the morning as whole capsules or sprinkled on a small amount of applesauce.[8]

The initial dosage in patients not currently receiving dexmethylphenidate IR or racemic MPH, or who are receiving other stimulants, is 5 mg/day for paediatric patients and 10 mg/day for adult patients.[8] In patients currently using MPH, the recommended starting dose of dexmethylphenidate XR is half the total daily dose of racemic MPH; patients currently receiving dexmethylphenidate IR may be switched to the same total daily dose of dexmethylphenidate XR.

Dosage may be adjusted weekly in 5mg increments in paediatric patients and in 10mg increments in adults to a maximum of 20 mg/day.[8]

Paediatric patients on long-term therapy should be carefully monitored and those that are not growing or gaining weight as expected should have their treatment interrupted.[8]

Local prescribing information should be consulted for dosage reduction guidelines in patients experiencing toxicity, dosage recommendations in special populations, contraindications and precautions.

6. Dexmethylphenidate Extended Release in Attention-Deficit Hyperactivity Disorder: Current Status

Dexmethylphenidate XR 5, 10 or 20 mg/day is approved in the US for the treatment of ADHD in patients aged ≥6 years.[8]

Once-daily oral dexmethylphenidate XR was more effective than placebo in reducing ADHD symptom scores in children, adolescents and adults with ADHD in four randomised, double-blind, placebo-controlled trials of up to 7 weeks' duration. Dexmethylphenidate XR was generally well tolerated, with adverse events similar to those observed with MPH.

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

References

1. Brown RT, Freeman WS, Perrin JM, et al. Prevalence and assessment of attention-deficit/hyperactivity disorder in primary care settings. Pediatrics 2001 Mar; 107 (3): E43

2. Wender PH, Wolf LE, Wasserstein J. Adults with ADHD. An overview. Ann N Y Acad Sci 2001 Jun; 931: 1-16

3. Kessler RC, Adler L, Ames M, et al. The prevalence and effects of adult attention deficit/hyperactivity disorder on work performance in a nationally representative sample of workers. J Occup Environ Med 2005 Jun; 47 (6): 565-72

4. Greenhill LL, Abikoff HB, Arnold LE, et al. Medication treatment strategies in the MTA Study: relevance to clinicians and researchers. J Am Acad Child Adolesc Psychiatry 1996 Oct; 35 (10): 1304-13

5. Srinivas NR, Hubbard JW, Quinn D, et al. Enantioselective pharmacokinetics and pharmacodynamics of *dl-threo*-methylphenidate in children with attention deficit hyperactivity disorder. Clin Pharmacol Ther 1992 Nov; 52 (5): 561-8

6. Keating GM, Figgitt DP. Dexmethylphenidate. Drugs 2002; 62 (13): 1899-904

7. Markowitz JS, Straughn AB, Patrick KS. Advances in the pharmacotherapy of attention-deficit-hyperactivity disorder: focus on methylphenidate formulations. Pharmacotherapy 2003 Oct; 23 (10): 1281-99

8. Novartis Pharmaceuticals Corporation. Focalin™ XR (dexmethylphenidate hydrochloride) extended-release capsules prescribing information [online]. Available from URL: http://www.fda.gov/cder/foi/label/2005/021802lbl.pdf [Accessed 2005 Oct 19]

9. Teo SK, Stirling DI, Thomas SD, et al. Neurobehavioral effects of racemic *threo*-methylphenidate and its D and L enantiomers in rats. Pharmacol Biochem Behav 2003 Feb; 74 (3): 747-54

10. Wigal S, Swanson JM, Feifel D, et al. A double-blind, placebo-controlled trial of dexmethylphenidate hydrochloride and *d,l-threo*-methylphenidate hydrochloride in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2004 Nov; 43 (11): 1406-14

11. Kimko HC, Cross JT, Abernethy DR. Pharmacokinetics and clinical effectiveness of methylphenidate. Clin Pharmacokinet 1999 Dec; 37 (6): 457-70

12. Findling RL, Dogin JW. Psychopharmacology of ADHD: children and adolescents. J Clin Psychiatry 1998; 59 (Suppl. 7): 42-9

13. Markowitz JS, Straughn AB, Patrick KS. Advances in the pharmacotherapy of attention-deficit-hyperactivity disorder: focus on methylphenidate formulations. Pharmacotherapy 2003 Oct; 23 (10): 1281-99

14. Silva RR, Lopez FA, Muniz R, et al. Once-daily dexmethylphenidate: a placebo-controlled crossover study in children with attention-deficit/hyperactivity disorder [poster]. 34th Annual Meeting of the Child Neurology Society; 2005 Sep 28-Oct 1; Los Angeles (CA)

15. Adler LA, McGough J, Muniz R et al. Long-term efficacy of extended release dexmethylphenidate in adult ADHD [abstract no. NR493 plus poster]. 158th Annual Meeting of the American Psychiatric Association; 2005 May 21-26; Atlanta (GA), 183-84

16. Spencer TJ, Kim S, Jiang H. Efficacy of dexmethylphenidate extended release capsules in adults with ADHD [abstract no. NR455 plus poster]. 157th Annual Meeting of the American Psychiatric Association; 2004 May 1-6; New York (NY), 170

17. Spencer TJ, Biederman J, Harding M, et al. Growth deficits in ADHD children revisited: evidence for disorder-associated growth delays? J Am Acad Child Adolesc Psychiatry 1996 Nov; 35 (11): 1460-9

18. 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 Dec; 56 (12): 1073-86

19. National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: changes in effectiveness and growth after the end of treatment. Pediatrics 2004 Apr; 113 (4): 762-9

20. Silva RR, Muniz R, Pestreich et al. Crossover study of dexmethylphenidate extended release [abstract no. NR489 plus poster]. 158th Annual Meeting of the American Psychiatric Association; 2005 May 21-26; Atlanta (GA), 182

21. Greenhil LL, Muniz R, Pestreich L, et al. Effective control of pediatric ADHD symptoms using once-daily dexmethylphenidate [poster no. C18]. 51st Annual Meeting of the American Academy of Child and Adolescent Psychiatry; 2004 Oct 19-24; Washington (DC)

22. Greenhill LL, Ball R, Levine AJ et al. Dexmethylphenidate extended release in children and adolescents with ADHD [abstract no. NR499 plus poster]. 158th Annual Meeting of the American Psychiatric Association; 2005 May 21-26; Atlanta (GA), 186

23. Markowitz JS, Patrick KS. Pharmacokinetic and pharmacodynamic drug interactions in the treatment of attention-deficit hyperactivity disorder. Clin Pharmacokinet 2001; 40 (10): 753-72

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