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Dexmethylphenidate

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Contents

Abstract

▲ Dexmethylphenidate comprises only the *d*-enantiomer (the pharmacologically effective isomer) of racemic methylphenidate and is indicated for the treatment of patients aged ≥6 years with attention deficit hyperactivity disorder (ADHD).

▲ In a 4-week, double-blind trial in 132 children with ADHD, significantly greater improvements from baseline in teacher-rated Swanson, Nolan and Pelham (SNAP)-ADHD scores were seen in dexmethylphenidate and methylphenidate recipients, compared with placebo recipients. In addition, significantly more dexmethylphenidate and methylphenidate recipients, compared with placebo recipients, were much improved or very much improved according to Clinical Global Impression-Improvement of Illness scale scores.

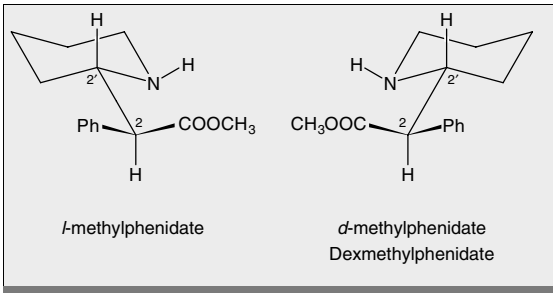
▲ In the same study, parent-rated SNAP-ADHD scores had decreased by a significantly greater extent in dexmethylphenidate recipients at 3pm and 6pm and in methylphenidate recipients at 3pm, compared with placebo recipients.

▲ Significantly fewer dexmethylphenidate than placebo recipients failed treatment in a double-blind, treatment-withdrawal trial in 75 children with ADHD (17.1 *vs* 61.5%).

▲ In a noncomparative study in 22 children with ADHD, symptoms of ADHD, as assessed by teachers and parents, were controlled during the entire school day in 68 and 86% of dexmethylphenidate recipients, respectively, with a median duration of effect of 6.3 and 7.5 hours, respectively.

▲ Dexmethylphenidate was generally well tolerated in children with ADHD; adverse events were consistent with those known to be associated with agents containing methylphenidate.

Features and properties of dexmethylphenidate	
Indication	
Attention deficit hyperactivity disorder in patients aged ≥6 years	
Mechanism of action	
Thought to block dopamine and noradrenaline (norepinephrine) reuptake into the presynaptic neuron	
Dosage and administration	
Patients not currently receiving methylphenidate	Initial dose of 2.5mg titrated to a maximum dosage of 20 mg/day
Patients currently receiving methylphenidate	Initial dosage of half that of racemic methylphenidate (maximum recommended dosage of 20 mg/day)
Route of administration	Oral
Frequency of administration	Twice daily (doses administered ≥4 hours apart)
Pharmacokinetic profile (dosage not specified)	
Time to peak plasma concentration	≈1 to 1.5 hours
Mean plasma elimination half-life	≈2.2 hours
Adverse events	
Most common	Abdominal pain, headache, anorexia, rhinitis



Isomers of racemic methylphenidate

Attention deficit hyperactivity disorder (ADHD) affects an estimated 4 to 12% of school-age children in the US.[1] The disorder is characterised by symptoms of inattention, hyperactivity and impulsivity.[2] Methylphenidate is the drug most commonly used in the treatment of children with ADHD.[3]

The *d*- and *l*-enantiomers of racemic methylphenidate are present in equal proportions, although the pharmacological efficacy of the drug is attributed solely to the *d*-enantiomer[4] (see section 1). Dexmethylphenidate comprises only the *d*-enantiomer of racemic methylphenidate (*d,l*-methylphenidate); this article focuses on the use of dexmethylphenidate in the treatment of children with ADHD.

1. Pharmacodynamic Profile

The pharmacodynamics of the *d*-enantiomer of methylphenidate have been examined in children with ADHD in a small crossover study.[4] Relevant data concerning the pharmacodynamics of methylphenidate are also included in this section.

• Dexmethylphenidate acts as a CNS stimulant and is thought to block dopamine and noradrenaline (norepinephrine) reuptake into the presynaptic neuron and increase neurotransmitter release into the extraneuronal space;[5] research is ongoing in this area.

• The pharmacodynamic activity of methylphenidate appears to reside entirely with the *d*-enantiomer. In a double-blind, randomised, crossover study, nine children (mean age 11.1 years) with ADHD received single doses of racemic methylphenidate 10mg, *d*-methylphenidate 5mg, *l*-methylphenidate 5mg and placebo on four study days separated by intervals of 1 week.[4] Mean scanning reaction time test scores (a measure of continuous performance) were significantly higher ($p < 0.005$) with racemic methylphenidate or *d*-methylphenidate, compared with *l*-methylphenidate or placebo, 1, 2 and 3 hours after drug administration. No significant differences between *d*-methylphenidate and racemic methylphenidate were seen with regards to this outcome.

• Methylphenidate has been associated with increases in heart rate and blood pressure, in keeping with its role as a CNS stimulant.[6-8] Small increases in heart rate (2 to 5 beats per minute) and blood pressure (2 to 3mm Hg) have been seen in patients receiving dexmethylphenidate in placebo-controlled studies;[5] the clinical significance of these effects is not known.

• There is concern that methylphenidate therapy may be associated with growth suppression as reductions in growth velocity and bodyweight have been seen in some studies; however, ultimate height and bodyweight do not appear to be compromised.[6,8,9] It has also been suggested that ADHD itself may be related to the observed growth suppression.[10] Data are not available concerning the effect of long-term dexmethylphenidate therapy on these parameters.[5]

2. Pharmacokinetic Profile

Most of the data in this section were obtained from the US prescribing information for dexmethylphenidate.[5] Information concerning the pharmacokinetics of racemic methylphenidate are also reported where relevant. No data are available concerning the use of dexmethylphenidate in patients with renal or hepatic impairment, or in children aged <6 years.

Absorption

• The maximum plasma dexmethylphenidate concentration (C_{max}) was reached (t_{max}) approximately 1 to 1.5 hours after administration of dexmethyl-

phenidate to patients with ADHD who were in a fasting state (dosage not stated).[5] In addition, no significant drug accumulation was seen after repeated, twice-daily administration of dexmethylphenidate to children with ADHD.

• In children, dose-proportional increases in C_{max} and the area under the plasma concentration-time curve (AUC_∞) were seen after administration of single doses of dexmethylphenidate 2.5, 5 and 10mg.[5] Moreover, plasma dexmethylphenidate concentrations achieved after administration of dexmethylphenidate were similar to those seen after administration of equimolar doses (i.e. twice the dose) of racemic methylphenidate.[5]

• Comparable C_{max} values were seen after administration of single doses of dexmethylphenidate (dosage not stated) to children aged 6 to 12 years and healthy adults. However, AUC values tended to be lower in children than in adults.[5]

• The pharmacokinetics of dexmethylphenidate were similar in boys and girls who received the drug (mean age 10 years).[5] Similarly, comparable t_{max} values were seen in adult female volunteers and adult male volunteers who received single doses of dexmethylphenidate 20mg.[5] However, bodyweight-adjusted AUC_∞ values were 25 to 35% higher in women, compared with men.

• In adults, administration of a single 20mg dose of dexmethylphenidate with food did not alter the C_{max} and AUC_∞ values obtained in the fasting state.[5] However, t_{max} was almost doubled when dexmethylphenidate 20mg was administered with a high-fat meal compared with in a fasting state (2.9 *vs* 1.5 hours).

Metabolism and Elimination

• Dexmethylphenidate is metabolised by de-esterification to its primary metabolite, *d*-α-phenyl-piperidine acetic acid (*d*-ritalinic acid), which has negligible pharmacological activity.[5] Dexmethylphenidate did not have an inhibitory effect on cytochrome P450 isoenzymes in *in vitro* studies.[5]

• Dexmethylphenidate has a mean elimination half-life ($t_{½}$) of approximately 2.2 hours.[5] No gender-related differences in $t_{½}$ were seen in children or adults who received dexmethylphenidate.[5]

• Following oral administration of radiolabelled racemic methylphenidate in humans, approximately 90% of the dose was recovered in urine. Approximately 80% of the dose comprised ritalinic acid, the main urinary metabolite.[5]

3. Therapeutic Trials

The clinical efficacy of dexmethylphenidate has been examined in three studies (available as abstracts and posters) in children with ADHD; two were double-blind, placebo-controlled studies and one was a noncomparative flexible-dose study. In a double-blind randomised study,[11-13] 132 patients aged 6 to 17 years received dexmethylphenidate (initial dosage of 2.5mg twice daily titrated to a maximum of 10mg twice daily; n = 44), methylphenidate (initial dosage of 5mg twice daily titrated to a maximum of 20mg twice daily; n = 46) or placebo (n = 42), for 4 weeks (doses were administered at 8am and 12pm each day). In a multicentre treatment-withdrawal study,[14] 75 patients aged 6 to 17 years who had responded to dexmethylphenidate during a 6-week nonblind treatment period received dexmethylphenidate (dosage not stated; n = 35) or placebo (n = 40) in a double-blind manner during a 2-week withdrawal phase. In a noncomparative flexible-dose study,[15] 22 patients (six of whom had previously been treated with other stimulants and had not achieved a good response) received dexmethylphenidate 2.5 to 30mg once daily in the morning for 8 weeks (patients were aged between 6 and 12 years).

The primary endpoint in the larger double-blind study[11] was the reduction from baseline in teacher-rated Swanson, Nolan and Pelham (SNAP)-ADHD Rating Scale scores; secondary endpoints included SNAP-ADHD Rating Scale scores as rated by parents at 3 and 6pm and Clinical Global Impression-Improvement of Illness (CGI-I) scale scores. The SNAP-ADHD Rating Scale is an 18-item scale, scored from 0 to 3, that assesses ADHD symptoms. In the double-blind treatment-with-

drawal study,[14] the primary endpoint was the proportion of patients who had failed treatment at the end of the 2-week withdrawal phase. Treatment failure was defined as a CGI-I score (as rated by the investigator) of much worse or very much worse. The math test score at the end of the withdrawal phase was a secondary endpoint.[14] In the noncomparative study,[15] the primary endpoint was the reduction from baseline in Teacher and Parent Conners Rating Scale scores; secondary endpoints included teacher- and parent-rated Visual Analogue Scale scores.

• Dexmethylphenidate improved the symptoms of ADHD by a similar extent to methylphenidate in the larger double-blind trial.[11] After 4 weeks' treatment, significantly greater reductions from baseline in mean teacher-rated SNAP-ADHD scores were seen in dexmethylphenidate (from 1.4 to 0.8 points; p = 0.0004 *vs* placebo) and methylphenidate (from 1.8 to 0.9 points; p = 0.0042 *vs* placebo) recipients than in placebo recipients (from 1.6 to 1.4 points).[11] Similarly, according to last observation carried forward analysis, significantly greater mean reductions from baseline in teacher-rated SNAP-ADHD scores were seen in dexmethylphenidate (p < 0.0001) and methylphenidate (p = 0.0015) recipients, compared with placebo recipients (figure 1).[12] It is notable that this improvement was achieved with a maximum allowable dexmethylphenidate dosage that was half that of methylphenidate.

• In addition, mean parent-rated SNAP-ADHD scores at 3pm had decreased by a significantly greater extent in dexmethylphenidate (p < 0.001) and methylphenidate (p < 0.0073) recipients than in placebo recipients (figure 1).[11,13] However, at 6pm, the reduction in mean parent-rated SNAP-ADHD scores was significantly greater in dexmethylphenidate than in placebo recipients (p = 0.003), but not in methylphenidate recipients (figure 1).[11,13] These data suggest a potential trend towards a longer duration of action for dexmethylphenidate compared with methylphenidate.

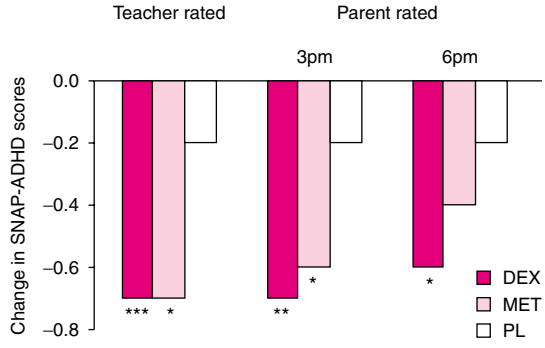


Fig. 1. Changes from baseline in mean teacher- and parent-rated SNAP-ADHD scores in children (aged 6 to 17 years) with ADHD. In this double-blind, randomised study, 132 children were randomised to receive twice-daily dexmethylphenidate (DEX; n = 44), methylphenidate (MET; n = 46) or placebo (PL; n = 42) for 4 weeks.[11-13] Changes in teacher-rated SNAP-ADHD scores are means (LOCF analysis). Changes in mean parent-rated SNAP-ADHD scores were assessed at 3pm and 6pm. **ADHD** = attention deficit hyperactivity disorder; **LOCF** = last observation carried forward analysis; **SNAP** = Swanson, Nolan and Pelham; * p < 0.01, ** p < 0.001, *** p < 0.0001 vs PL.

• Moreover, significantly more dexmethylphenidate recipients (p < 0.0001) and methylphenidate recipients (p = 0.0082), compared with placebo recipients, were much improved or very much improved according to CGI-I scores (65.9 and 46.7 *vs* 19.5%).[11]

• Significantly fewer treatment failures were seen with dexmethylphenidate compared with placebo therapy in the double-blind treatment-withdrawal study (17.1 *vs* 61.5%; p = 0.001).[14] In addition, compared with the end of the nonblind phase, mean math test scores improved in dexmethylphenidate recipients and worsened in placebo recipients (+1 *vs* –12; values estimated from graph) [p = 0.024].

• Once-daily administration of dexmethylphenidate was associated with significant improvements from baseline in ADHD symptoms in the noncomparative study.[15] Mean Teacher and Parent Conners Rating Scale scores were significantly reduced from baseline (p < 0.0001) by 66 and 52%, respectively, after 8 weeks' treatment with dex-

methylphenidate (figure 2). According to teacher- and parent-rated Visual Analogue Scale scores, the symptoms of 68 and 86% of patients, respectively, were controlled during the entire school day. The median duration of effect was 6.3 (range 4 to 7.5) and 7.5 (range 5 to 14) hours as assessed by teachers and parents, respectively. Of the six patients who had previously been treated unsuccessfully with stimulants, five responded to dexmethylphenidate therapy (definition of response not stated). It should be noted that current labelling states that dexmethylphenidate should be administered twice daily with an interval of at least 4 hours between doses (section 5).

4. Tolerability

• Dexmethylphenidate was generally well tolerated in children with ADHD;[11,14,15] adverse events were consistent with those known to be associated with agents containing methylphenidate.

• In a 4-week, double-blind, randomised, placebo-controlled study in 132 children (aged 6 to 17 years) with ADHD, adverse events tended to occur more frequently in recipients of active treatment compared with placebo.[11] Abdominal pain occurred in 20.5, 4.3 and 11.9% of dexmethylphenidate, methylphenidate and placebo recipients, respectively, headache occurred in 15.9, 21.7 and 9.5%, respectively, anorexia occurred in 9.1, 10.9 and 0%, respectively, and rhinitis occurred in 15.9, 4.3 and 9.5%, respectively. No serious adverse events were reported in this study.

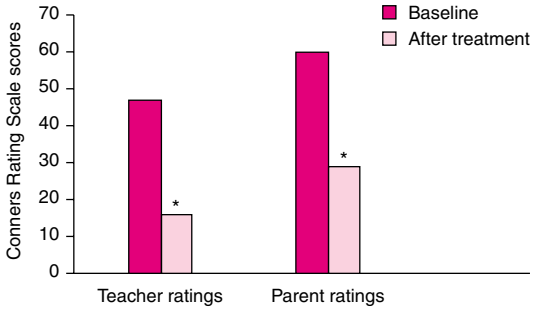


Fig. 2. Mean Teacher and Parent Conners Rating Scale scores in 22 children (aged 6-12 years) with attention deficit hyperactivity disorder in a noncomparative, flexible-dose study.[15] Children received dexmethylphenidate 2.5 to 30mg once daily for 8 weeks.* $p < 0.0001$ *vs* baseline.

• Similarly, no serious treatment-related adverse events were reported in a double-blind, placebo-controlled, treatment-withdrawal study in 75 patients (aged 6 to 17 years) with ADHD.[14] During the double-blind phase of the trial, abdominal pain occurred in 8.6% of dexmethylphenidate recipients and 0% of placebo recipients, chest pain in 5.7 and 0%, headache in 5.7 and 7.5%, insomnia in 0 and 5.0%, increased cough in 5.7 and 0% and rhinitis in 0 and 5.0%.

• In a noncomparative study in 21 evaluable patients (aged 6 to 12 years) with ADHD, the most commonly occurring adverse events included anorexia or weight loss (33%), lability (19%), stomachache or nausea (14%), headache (14%) and sullenness (10%).[15] Flushed face, sedation, irritability, monotone voice, staring and nightmares each occurred in 5% of patients. Patients in this study received dexmethylphenidate 2.5 to 30mg once daily for 8 weeks.

5. Dosage and Administration

• In patients with ADHD who are not currently receiving methylphenidate, or are receiving other stimulants, treatment with dexmethylphenidate should be started at a dosage of 2.5mg twice daily and titrated at 2.5 to 5mg increments to a maximum daily dose of 20mg. In general, dosage adjustments may occur at intervals of about 1 week.[5] In patients who are currently receiving methylphenidate, dexmethylphenidate should be started at a dosage of half that of methylphenidate; the dosage can be titrated to a maximum of 20 mg/day. The two daily doses of dexmethylphenidate should be administered at least 4 hours apart; the drug may be administered with or without food. Dexmethylphenidate is available as 2.5, 5 and 10mg tablets.

6. Dexmethylphenidate: Current Status

Dexmethylphenidate is approved for the treatment of ADHD in children aged ≥6 years in the US and is currently awaiting approval in Canada. It was associated with significant improvements in ADHD symptoms in children in a randomised, double-blind study and in a noncomparative study. In addition, significantly fewer dexmethylphenidate than placebo recipients failed treatment in a double-blind, multicentre, treatment-withdrawal trial. Dexmethylphenidate was generally well tolerated with an adverse event profile similar to that expected with agents containing methylphenidate.

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