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Extended-Release Methylphenidate (Ritalin® LA[1])

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Contents

Abstract

▲ An extended-release formulation of methylphenidate (Ritalin® LA), a CNS stimulant that inhibits dopamine and noradrenaline (norepinephrine) reuptake into presynaptic neurons, has been developed for use in patients with attention deficit/hyperactivity disorder (ADHD).

▲ In children with ADHD and healthy male adults, extended-release methylphenidate 20mg was rapidly absorbed and demonstrated two distinct peak plasma concentrations ≈4 hours apart. The absorption pharmacokinetics of extended-release methylphenidate 20mg, which closely mimics those of immediate-release methylphenidate 10mg given in two doses 4 hours apart, permits once-daily administration.

▲ In a 2-week randomised, double-blind, placebo-controlled trial in 134 evaluable children aged 6 to 12 years with ADHD, symptoms improved to a significantly greater extent with extended-release methylphenidate 10 to 40mg once daily than with placebo.

▲ Extended-release methylphenidate improved both inattention and hyperactivity symptoms and was effective in children with combined- (inattentive and hyperactive/impulsive) type or predominantly inattentive-type ADHD.

▲ In clinical trials, the safety and tolerability profiles of extended-release methylphenidate were consistent with that of the immediate-release formulation.

Features and properties of extended-release methylphenidate (Ritalin® LA)	
Indication	
Attention deficit/hyperactivity disorder in patients aged ≥6 years	
Mechanism of action	
May be due to inhibition of dopamine and noradrenaline (norepinephrine) reuptake into the presynaptic neuron	
Dosage and administration	
Previously untreated patients	Initial dosage of 20 mg/day titrated to a maximum dosage of 60 mg/day
Previously treated patients	20 to 60 mg/day depending on the previous dosage of methylphenidate
Route of administration	Oral
Frequency of administration	Once daily in the morning
Pharmacokinetic profile (20mg single dose)	
First peak plasma concentration (C_{max1})	10.3 μg/L (children); 5.3 μg/L (adults)
Time to C_{max1}	2.0h (children); 2.0h (adults)
Second peak plasma concentration (C_{max2})	10.2 μg/L (children); 6.2 μg/L (adults)
Time to C_{max2}	6.6h (children); 5.5h (adults)
Area under the plasma concentration-time curve extrapolated to infinity	86.6 μg • h/L (children); 45.8 μg • h/L (adults)
Plasma elimination half-life	2.4h (children); 3.3h (adults)
Most frequent adverse events	
Headache, insomnia, upper abdominal pain, decreased appetite, anorexia and nasopharyngitis	

1 Use of a tradename is for product identification purposes only, and does not imply endorsement.

Children with attention deficit/hyperactivity disorder (ADHD), the most extensively studied neurobehavioural disorder of childhood, show symptoms that include inattention, underperformance, hyperactivity and impulsiveness.[1,2] This disorder, which presents in childhood and may continue through adolescence and adult life, may result in functional problems such as poor interpersonal relationships, difficulties in school and underachievement in careers.[1,3] ADHD is effectively treated with stimulant medication (e.g. methylphenidate) and/or behaviour therapy.[2,4-6] However, the short duration of action of immediate-release methylphenidate results in the drug often being administered two to three times daily,[4,6,7] which may present problems with administration of the midday dose during school hours.[6,8,9]

A number of formulations of extended-release methylphenidate are available; this review examines the use of a novel once-daily extended-release formulation of methylphenidate (Ritalin® LA), hereafter referred to as extended-release methylphenidate, in the treatment of ADHD. This formulation uses a spheroidal oral drug absorption system (SODAS™), which allows 50% of the drug (formulated as immediate-release beads) to be released immediately providing a rapid onset, and 50% (formulated as enteric-coated delayed-release beads) to be released ≈4 hours after administration.[9] This mimics the twice-daily administration of immediate-release methylphenidate.

1. Pharmacodynamic Profile

The pharmacodynamic profile of methylphenidate in patients with ADHD has been reviewed elsewhere.[7,10,11] This section provides a brief overview of the pharmacodynamic properties of methylphenidate with a focus on the extended-release formulation.

Mechanism of Action

- Although the mechanism of action of methylphenidate in ADHD is not well established, it may be attributable in part to the inhibition of dopamine reuptake.[9] The drug, a CNS stimulant, blocks the transporter for dopamine and, to some extent, noradrenaline (norepinephrine), resulting in the inhibition of reuptake of these monoamines into the presynaptic neuron.[9,11,12] After oral administration of methylphenidate and intravenous administration of [^{11}C] cocaine (a dopamine transporter ligand) in adult volunteers, positron emission tomographic scans showed occupation of the dopamine transporter in the striatal area of the brain by methylphenidate.[13]
- Patients with ADHD appear to have increased numbers of dopamine transporters compared with healthy volunteers,[14,15] which indicates the blocking of the dopamine transporter by methylphenidate and the resulting normalisation of dopamine levels may play a role in its therapeutic efficacy.
- The blockade of dopamine and, putatively, noradrenaline transporters by methylphenidate and the resulting reuptake inhibition increases the amount of these monoamines in the extraneuronal space.[6,9] This increase in the amount of dopamine in the extraneuronal space may enhance cognitive and behavioural responses in patients with ADHD.[6]

Effects on ADHD Symptoms in Children

Cognitive and behavioural responses were measured in 34 children aged 6 to 12 years with combined inattentive and hyperactive/impulsive ADHD who received a single dose of four different dose/formulation variants of extended-release methylphenidate and placebo in a multicentre, randomised, double-blind, 5-period crossover study.[9,16] Data (reported as a poster[16] and in the product monograph[9]) are presented for the 20mg dose of extended-release methylphenidate. This was the optimal variant in the trial because its rapid onset and duration of action closely resembled those of immediate-release methylphenidate twice daily. Patients were already receiving treatment with immediate-release methylphenidate 10mg two or three times daily and continued to receive their usual dosage of methylphenidate between each treatment evaluation. Evaluation of the time-

course effects of each treatment took place at baseline and at various timepoints up to and including ≈9 hours postdose.[9]

- Significantly better behavioural and cognitive responses were shown in children with ADHD receiving extended-release methylphenidate 20mg (n = 32) than in those receiving placebo (n = 32) throughout the evaluation period ($p \leq 0.05$ for all comparisons), including the periods 0 to 9 hours postdose (figure 1), in the morning (0 to 4 hours postdose) and afternoon (4 to 9 hours postdose; figure 1).[9,16] This was assessed by the mean area under the curve for Swanson, Kotkin, Angler, M-Flynn and Pelham (SKAMP)-attention or -deportment factor subscale scores;[17] lower SKAMP subscale scores and area-under-the-curve values are consistent with less impairment.
- Patients receiving extended-release methylphenidate 20mg both attempted and answered correctly significantly more mathematics problems than patients receiving placebo ($p < 0.001$ for both), demonstrating improvements in attention and concentration.[9,16]

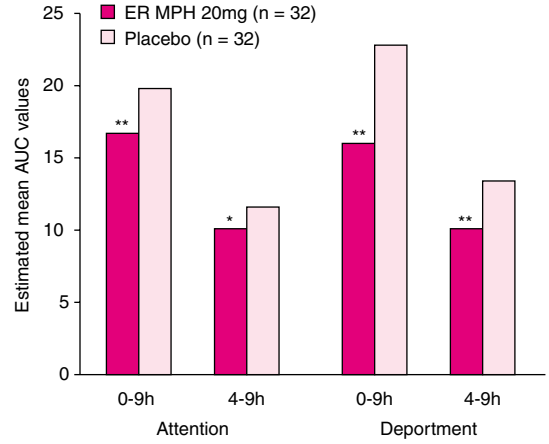

Fig. 1. Effects of single-dose extended-release methylphenidate (ER MPH) 20mg in children with attention deficit/hyperactivity disorder (ADHD). Estimated mean area-under-the-curve (AUC) values 0 to 9 or 4 to 9 hours postdose for Swanson, Kotkin, Angler, M-Flynn and Pelham (SKAMP)-attention or -deportment factor subscale scores after single-dose treatment in the morning with ER MPH 20mg or placebo.[9,16] Results are from a multicentre, randomised, double-blind, 5-period crossover study in children aged 6 to 12 years with combined inattentive and hyperactive/impulsive ADHD who were already receiving immediate-release methylphenidate 10mg twice daily. A lower value is consistent with less impairment. * $p \leq 0.05$, ** $p \leq 0.001$ vs placebo.

Systemic Effects

- In the 2-week, double-blind, placebo-controlled efficacy trial in children with ADHD (section 3), patients receiving extended-release methylphenidate had smaller mean weight gains than patients receiving placebo (0.1 *vs* 1.0kg).[9] Although reductions in growth velocity have been noted in some studies involving children receiving methylphenidate,[18,19] this effect appears to be associated with ADHD and not with its treatment.[18] Height may normalise by late adolescence[18] and ultimate adult height is generally not compromised.[20,21]
- Although increases in blood pressure and pulse were not evaluated in the pharmacodynamic[9,16] and efficacy trials,[9,22,23] these effects have been associated with treatment with methylphenidate.[9,24,25] In general, these increases are clinically insignificant.[25]
- Some clinical evidence suggests that the seizure threshold may be lowered with methylphenidate in patients with history of seizures, in patients with a history of EEG abnormalities but not seizures and, very rarely, in patients with no history of seizures or EEG abnormalities.[9,26] However, other studies have not shown an increase in seizure frequency with methylphenidate in patients with seizure disorders,[27] ADHD plus seizure disorders well controlled by anticonvulsants,[28,29] or ADHD and a normal EEG.[30] Nevertheless, the manufacturer recommends discontinuing extended-release methylphenidate in the presence of seizures.[9]

2. Pharmacokinetic Profile

Methylphenidate is released from this extended-release formulation in a bimodal fashion; the first release, which is rapidly absorbed, occurs immediately after administration, and the second occurs ≈4 hours after administration.[9] Therefore, the pharmacokinetic profile of single-dose extended-

release methylphenidate 20mg has been compared with that of two doses of immediate-release methylphenidate 10mg given 4 hours apart. Unless otherwise noted, pharmacokinetic values in this section are from 18 children aged 7 to 12 years with ADHD or 8 healthy adult males who received single-dose extended-release methylphenidate 20mg, and from 21 children aged 7 to 12 years with ADHD or 9 healthy adult male who received two doses of methylphenidate 10mg 4 hours apart. The results of these studies are reported in the product monograph of the drug.[9] The pharmacokinetics of extended-release methylphenidate have not been studied in children aged <6 years.

Absorption and Distribution

• In children and adults, extended-release methylphenidate is rapidly absorbed, with the first peak plasma concentration (C_{max1}) reached within 2.0 hours (t_{max1}) and an absolute bioavailability of ≈30%.[9] Mean t_{max1} and bioavailability of the extended-release formulation are similar to those of the same total dose of immediate-release methylphenidate given as two doses 4 hours apart (mean t_{max1} 1.8 or 1.9 hours in children or adults).

• Extended-release methylphenidate 20mg demonstrated a second distinct mean peak plasma concentration (C_{max2}) ≈4 hours after C_{max1} (t_{max2}) [figure 2]. Mean values for t_{max2} and the area under the plasma concentration-time curve extrapolated to infinity (AUC_∞) were 6.6 hours and 86.6 μg • h/L in children (n = 15 for mean AUC_∞ value) or 5.5 hours and 45.8 μg • h/L in adults.[9] In comparison, when immediate-release methylphenidate 10mg was given in two doses 4 hours apart, mean t_{max2} values in children or adults were 5.6 or 5.9 hours after administration of the first dose, and mean AUC_∞ values were 102.4 or 37.8 μg • h/L.

• In a study in healthy adults, mean C_{max1} was ≈12.5 μg/L with either single-dose extended-release methylphenidate 40mg (n = 17) or two doses of immediate-release methylphenidate 20mg given 4 hours apart (n = 16); mean C_{max2} was lower with the extended-release formulation than with the immediate-release formulation (≈14 *vs* ≈18.5 μg/L) [C_{max} values estimated from a figure].[9] This indicated that peak and trough fluctuations were less with extended-release methylphenidate 40mg than immediate-release methylphenidate 20mg twice daily.

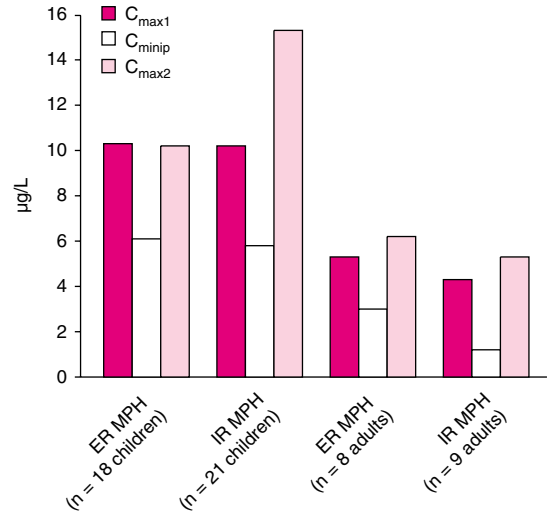

Fig. 2. Mean plasma concentrations of methylphenidate after a single dose of extended-release methylphenidate 20mg (ER MPH) or two doses of immediate-release methylphenidate 10mg given 4 hours apart (IR MPH).[9] The figure shows the first and second peak plasma concentrations (C_{max1} and C_{max2}) and minimum interpeak plasma concentrations (C_{minip}) for ER MPH and IR MPH in children with attention deficit/hyperactivity disorder and healthy male adults.

• The smaller body size and smaller total volume of distribution in children accounts for the approximately 2-fold higher C_{max1} and C_{max2} values of extended-release methylphenidate 20mg in children compared with adults (figure 2).[9] AUC, C_{max1} and C_{max2} are dose proportional in children and adults.[9]

• For both formulations of methylphenidate, peak plasma concentrations vary substantially between individuals.[9] The range of variation is greater in children than in adults and is generally greater with extended-release methylphenidate than with immediate-release methylphenidate.

• Compared with adults, children also showed greater variation and longer delays in the time to

minimum interpeak plasma concentrations (t_{minip}) and t_{max2} with extended-release methylphenidate.[9] In children, mean t_{minip} was 4.5 hours (range 2 to 6 hours) and mean t_{max2} was 6.6 hours (range 5 to 11 hours). In adults, mean t_{minip} and mean t_{max2} were 3.6 (range 2.7 to 4.3 hours) and 5.5 hours (range 4.3 to 6.5 hours).

- Compared with administration under fasting conditions, administration of extended-release methylphenidate with a high-fat breakfast in healthy adults delayed the absorption of the drug, which increased t_{max1} and t_{max2} (study details not given).[9] Although no changes in C_{max1} or extent of absorption of extended-release methylphenidate were demonstrated, C_{max2} decreased by approximately one-quarter. Importantly, administration of extended-release methylphenidate with apple sauce (a suggested method of administering the drug; section 5) did not change the pharmacokinetics of the drug compared with administration under fasting conditions.
- The distribution of methylphenidate and its metabolites in blood is 57% in plasma and 43% in erythrocytes.[9] Ten to 33% of the drug and its metabolites are bound to plasma proteins. The steady-state apparent volume of distribution of extended-release methylphenidate was 6 L/kg after intravenous administration (study details not given).

Metabolism and Elimination

- De-esterification by nonmicrosomal hydrolytic esterases, which are widely distributed throughout the body, is the predominant metabolic pathway of methylphenidate.[7,9,10,31] It is primarily metabolised to α-phenyl-2-piperidine acetic acid (ritalinic acid), which has little to no pharmacological activity.[7,31] Metabolites (e.g. hydroxymethylphenidate and hydroxyritalinic acid) formed from minor pathways (e.g. aromatic hydroxylation, microsomal oxidation and conjugation) also appear to have little pharmacological activity.[7]
- The mean elimination half-life from plasma ($t_{½}$) of extended-release methylphenidate was longer in adults than in children (n = 15) [3.3 *vs* 2.4 hours].[9] These values were comparable to the mean $t_{½}$ of immediate-release methylphenidate in each corresponding patient group (3.5 hours in adults and 2.5 hours in children).
- Oral methylphenidate was eliminated primarily in the form of metabolites in the urine (78 to 97% of the dose) and faeces (1 to 3%) within 48 to 96 hours of administration (study details not given).[9] Less than 1% of the radiolabelled dose was accounted for by unmetabolised methylphenidate in the urine. The predominant metabolite in the urine was ritalinic acid (60 to 86%).

In Patients with Renal or Hepatic Dysfunction

- The pharmacokinetics of extended-release methylphenidate have not been studied in patients with renal or hepatic insufficiency.[9] However, the pharmacokinetics of methylphenidate should be minimally affected by renal insufficiency (because of the small amount of the dose that is excreted unchanged in the urine and the inactivity of the major metabolite)[7,9,31] or hepatic insufficiency (because primary metabolism is by nonmicrosomal hydrolytic esterases).[9]

Potential for Drug Interactions

- Coadministration of monoamine oxidase inhibitors (MAOIs) and methylphenidate may result in hypertensive crisis.[9,10] Therefore, the concomitant use of these drugs, or the use of methylphenidate within 14 days of discontinuing treatment with an MAOI, is contraindicated.[9]
- Methylphenidate may interact with drugs that have an effect on blood pressure (e.g. $α_2$-agonists and vasoconstrictor agents).[9,10,32] Because methylphenidate increases the concentration of noradrenaline at postsynaptic receptors and blocks uptake of guanethidine (a post-ganglionic adrenergic blocking agent), the hypotensive effect of guanethidine may be decreased or entirely blocked by methylphenidate.[10,33] Caution is advised when coadministering methylphenidate and drugs that affect blood pressure.[9]
- Concomitant administration of clonidine (which may be useful in the treatment of sleep dis-

turbances, aggressive behaviour or conduct disorder in certain children with ADHD)[32] plus extended-release methylphenidate has resulted in adverse cardiovascular events and/or death.[9,34,35] Causality between the adverse events and the drug combination has not been established;[9,10] nevertheless, caution is advised when these drugs are coadministered to patients with cardiovascular disease.[34]

- The metabolism of coumarin anticoagulants, tricyclic antidepressants (e.g. imipramine, clomipramine, desipramine), and anticonvulsants (e.g. phenobarbital, phenytoin) may be inhibited by methylphenidate.[9,10,33] Therefore, the dosage of these drugs may need to be decreased when concomitant treatment with methylphenidate is initiated or increased when methylphenidate treatment is discontinued.
- The release of methylphenidate from the extended-release formulation may be altered when the drug is administered with alkalinising (e.g. antacids or acid suppressants) or acidifying (e.g. high-dose ascorbic acid) agents.[9,10,32,33] The release of extended-release methylphenidate from this formulation is dependent on pH; however, studies have not been conducted on the effect of altering gastrointestinal pH on the absorption of the drug.
- Methylphenidate does not alter the pharmacokinetics of drugs metabolised by cytochrome P450.[10]

3. Therapeutic Trial

The efficacy of once-daily extended-release methylphenidate compared with placebo has been evaluated in the treatment of 134 children aged 6 to 12 years with ADHD (as diagnosed by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV])[1] in a randomised, double-blind multicentre trial presented as an abstract,[22] a poster,[23] and in the product monograph.[9] Children received either their optimal dosage of extended-release methylphenidate (10, 20, 30 or 40 mg/day) or placebo once daily in the morning for up to 2 weeks, after a 2- to 4-week titration period and a 1-week placebo washout period.

The primary efficacy measure was the change from baseline in the Conners ADHS/DSM-IV Subscales for Teachers (CADS-T) total subscale score, assessed weekly by teachers during the school day.[9,22,23] Secondary measures were the change from baseline in the Conners ADHD/DSM-IV Subscales for Parents (CADS-P), assessed by parents on the weekends, the investigator-based Clinical Global Impression of Improvement (CGI-I) scale and the DSM-IV Inattention or Hyperactive-Impulsive subscales of the CADS-T or CADS-P.[9,23]

The efficacy of extended-release methylphenidate in the treatment of ADHD has not been compared with that of other methylphenidate formulations or other stimulants in clinical trials.

- Primary and secondary efficacy measures of ADHD improved to a significantly greater extent with extended-release methylphenidate than with placebo during the 2 weeks of treatment ($p < 0.05$ for all comparisons).[9,22,23] Extended-release methylphenidate was statistically superior to placebo regardless of whether the assessment was performed by teachers, parents or investigators.
- According to teacher assessments, 63 patients receiving extended-release methylphenidate demonstrated a significantly greater change from baseline in CADS-T total subscale score than 71 placebo recipients ($p < 0.0001$) [figure 3].[9,23] Moreover, extended-release methylphenidate was effective both in patients with combined (inattentive and hyperactive/impulsive) -type ADHD ($n = 100$; $p < 0.0001$) and in patients with predominantly inattentive-type ADHD ($n = 26$; $p < 0.05$) [figure 3].
- Inattention and hyperactivity improved to a significantly greater extent with extended-release methylphenidate than with placebo in teacher assessments.[9,23] Both inattentive and hyperactive subscale scores of the CADS-T demonstrated mean improvements of 5.3 and 5.4 points from baseline values with extended-release methylphe-

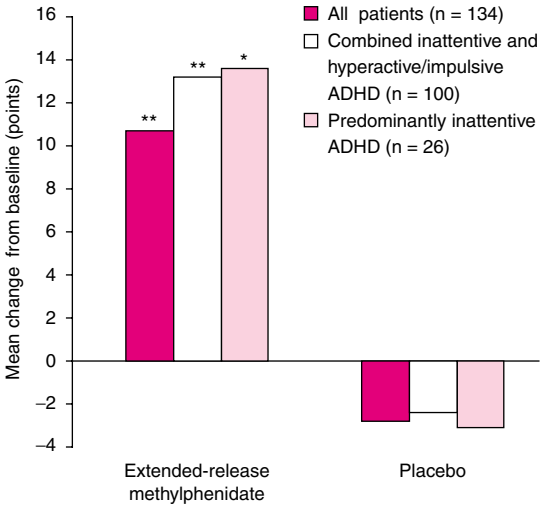

Fig. 3. Effect of extended-release methylphenidate in 134 evaluable children with attention deficit/hyperactivity disorder (ADHD). Mean changes from baseline values in the Conners ADHD/DSM-IV Subscales for Teachers (CADS-T) total subscale score after 2 weeks' treatment with once-daily, morning dosages of either extended-release methylphenidate at the optimal dosage for each patient (i.e. 10, 20, 30 or 40 mg/day) [n = 63] or placebo (n = 71).[9,23] Results are from a randomised, double-blind, multicentre trial in children aged 6 to 12 years with ADHD and include data from patients who had undergone at least one post-baseline evaluation of the CADS-T. An increase in score is consistent with an improvement in symptoms. * $p < 0.05$, ** $p < 0.0001$ *vs* placebo.

nidate compared with mean changes of –1.5 and –1.3 points from baseline with placebo ($p < 0.001$).

• Likewise, in parent assessments, extended-release methylphenidate showed greater mean improvements from baseline values in CADS-P scores than placebo.[9,23] Mean CADS-P total subscale scores improved by 6.3 points from baseline values in patients receiving extended-release methylphenidate compared with an improvement of 0.5 points in patients receiving placebo ($p = 0.0043$). Extended-release methylphenidate also improved both mean inattentive and hyperactive subscale scores to a significantly greater extent than placebo [2.8 *vs* 0.2 points ($p = 0.0213$) and 3.5 *vs* 0.3 points ($p = 0.0015$)].

• In investigator assessments using the CGI-I scale, significantly more patients who received extended-release methylphenidate were considered responders to treatment than patients who received placebo (69.8 *vs* 40.0% of patients; $p = 0.0009$).[9,23] Patients were considered to have responded to treatment if the final CGI-I score was ≤3 (on a scale of 1 to 7 where 1 indicates a very much improved condition, 3 a minimally improved condition, and 7 a very much worse condition).[9]

4. Tolerability

The tolerability profile of extended-release methylphenidate 10 to 40 mg/day was consistent with that of immediate-release methylphenidate in two clinical trials in 195 children with ADHD aged 6 to 12 years (sections 1 and 3)[16,22,23] and four pharmacology studies in 61 healthy adult male volunteers (section 1).[9] Most adverse events were mild and there were no reports of adverse events which were previously unknown for stimulants. In general, methylphenidate is well tolerated; commonly reported adverse events, regardless of formulation, include nervousness, insomnia, decreased appetite, abdominal pain and headache.[9,26,36,37]

• When the incidence of the onset of adverse events during the 2- to 4-week titration, 1-week placebo washout and 2-week, randomised, double-blind treatment periods of the multicentre efficacy study in children with ADHD (section 3) are combined, headache, insomnia and abdominal pain were the most commonly reported adverse events (figure 4).[9] In the double-blind period of the efficacy trial, the incidence of adverse events is included only for patients receiving individually titrated extended-release methylphenidate 10 to 40 mg/day (n = 65) and not for those receiving placebo (n = 71).

• In patients receiving extended-release methylphenidate, the most common adverse events with an onset during the 2-week double-blind period of the efficacy study were anorexia, insomnia (3.1% of patients for each) and headache (1.5%).[9,23] In contrast, none of the patients in the placebo group reported anorexia or insomnia and 2% reported headache. A similar proportion of extended-re-

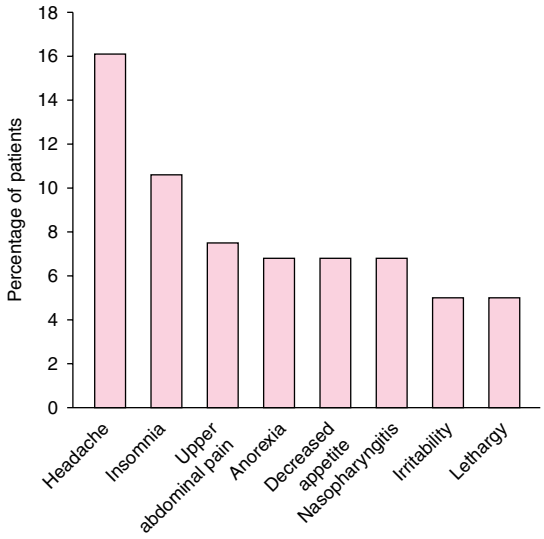

Fig. 4. Incidence of adverse events in children with attention deficit/hyperactivity disorder treated with extended-release methylphenidate 10 to 40 mg/day. The figure shows the onset of adverse events reported by ≥5% of evaluable patients aged 6 to 12 years receiving extended-release methylphenidate during the 2- to 4-week titration (n = 161), 1-week placebo washout (n = 138) and 2-week, randomised, double-blind treatment (n = 65) periods of a multicentre efficacy study.[9] The optimal dosage of extended-release methylphenidate for each patient was identified during the titration period. The incidence of adverse events with an onset during placebo treatment in the double-blind period of the trial is not included.

lease methylphenidate or placebo recipients experienced at least one treatment-emergent adverse event (24.6 *vs* 23.9%) during this period.[9,22,23]

- Six of 161 patients (3.7%) in the titration period and 1 of 64 patients (1.5%) in the double-blind period of the efficacy trial withdrew from the study because of adverse events.[9] Anger, hypomania, anxiety, depression, fatigue, migraine and lethargy were the adverse events leading to discontinuation.

5. Dosage and Administration

Extended-release methylphenidate (available as 20, 30 or 40mg capsules) should be administered orally as a single dose in the morning.[9] In previously untreated patients, treatment should be initiated at 20 mg/day and may be adjusted in 10mg increments at weekly intervals to a maximum dosage of 60 mg/day. In patients previously treated with other formulations of methylphenidate, the dosage should be individualised according to the previous dosage regimen. The capsules may be administered by swallowing whole or by sprinkling the capsule contents on a small amount of apple sauce and consuming the mixture immediately; the capsules should not be crushed, chewed or divided.

6. Extended-Release Methylphenidate: Current Status

The SODAS™ formulation of extended-release methylphenidate has been approved in the US for the treatment of ADHD in children aged ≥6 years. The immediate release of 50% of the dose provides a rapid onset of action; the release of the second 50% of the dose in ≈4 hours provides a duration of action that lasts throughout the school day. A recent, well controlled 2-week trial in children aged 6 to 12 years indicated that once-daily extended-release methylphenidate, at optimal individualised dosages, significantly improved symptoms of hyperactivity and inattention compared with placebo. The extended-release formulation of methylphenidate is generally well tolerated and has an adverse event profile consistent with that of immediate-release methylphenidate.

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