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ORIGINAL CONTRIBUTIONS

Long-acting medications for the hyperkinetic disorders

A systematic review and European treatment guideline

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Abstract A systematic review of published and unpublished data on the use of long-acting medications in ADHD and hyperkinetic disorder is reported, giving effect sizes and numbers-to-treat for extended-release stimulant preparations and atomoxetine (ATX). A panel of experts from several European countries used the review to make recommendations about the use of these drugs in practice, and conclusions are reported: (1) Long-acting preparations should be available and used; (2) They should not replace short-acting drugs (which will be the initial treatment for many children for reasons of cost and flexibility of dosing). Individual clinical choice is needed. (3) Both ATX and extended-release preparations of stimulants should be available. The choice will depend upon the circumstances, and detailed recommendations are made.

Key words guidelines – review – stimulants – atomoxetine – ADHD

ECAP 549

Introduction

Background

A group of European physicians and psychologists recently published guidelines for the treatment of hyperkinetic disorders [71]. There have been several developments in the field since then; one has been the advent of newly licensed drugs and drug preparations whose effect lasts through a substantial part of the day. This can overcome the inconveniences of the short-acting stimulants. A non-stimulant has been licensed, and often is in use. All, however, entail increased costs, and the choice among them can be confusing. This paper provides a review of their use.

The previous guidelines for the treatment of hyperkinetic disorders are still valid: a comprehensive treatment programme should include measures other than medicines—such as psychological, educational and social interventions. Treatment should be initiated under the supervision of a specialist in childhood behavioural disorders. Diagnosis should be made in accordance with DSM-IV criteria or the guidelines in ICD-10 and should be based on a full history and evaluation of the patient. Pharmacotherapy is not indicated for all children with this syndrome and the decision to use any of the drugs must be based on a thorough assessment of the severity, impact and developmental appropriateness of the child's symptoms. The current paper should be seen as a supplement to these recommendations.

Methodology of the review and guideline development

A group of experienced academic clinicians and clinical researchers with special interests in the hyperkinetic disorders was identified through the *European Network for Hyperkinetic Disorders* (EUNETHYDIS). Systematic reviews by NICE [30] and SIGN [54] were recent and available, and formed the basis for identifying published papers on methylphenidate, dexamfetamine and atomoxetine (ATX). Faraone's meta-analyses [12, 14, 15] were also referred to. Pharmaceutical companies with long-acting drugs in their portfolios were asked to provide unpublished as well as published data and posters (but information in commercial confidence was not included). The companies also presented at a meeting in September 2005 held in London. The calculation of effect sizes was carried out using a standard methodology. Where companies provided calculations of effect sizes using the standard methodology these were employed. If companies did not provide calculations using the standard methodology they were calculated by the authors.

The review and guideline development process was iterative. The identification of clinical questions was carried out in a meeting of all the authors, and a working group (TB, DC, SP, AZ) made a systematic review of published and unpublished clinical trials incorporating long-acting preparations; a quantitative review of the relevant data is reported below. Further meetings critiqued these reviews and their conclusions. A quantitative methodology for resolving disagreements had been anticipated (including an assessment of competing-interest information); but in the event, conclusions were unanimous. Drafts of the paper were exchanged and discussed iteratively. The final document is subscribed to by all the authors. The paper includes both a narrative summary of conclusions and a scientific examination of the data in two separate sections.

Narrative review and recommendations

Description of the drugs

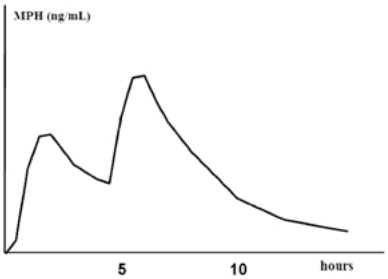
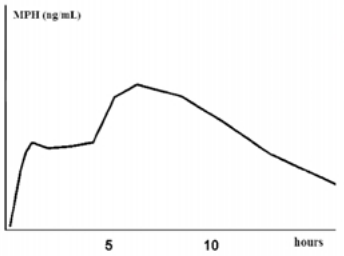
Stimulants

Methylphenidate hydrochloride

Methylphenidate hydrochloride (MPH) is a mild central nervous system (CNS) stimulant with more prominent effects on mental than motor activities. Its use in the treatment of hyperkinetic disorder and other forms of ADHD is well established and has been reviewed by EUNETHYDIS for *European Child and Adolescent Psychiatry* [71]. It is licensed in most European countries as part of comprehensive treatment programmes in children (over 6) and adolescents when remedial measures alone prove insufficient. *Ritalin LA* (Novartis), *Equasym XL* (UCB), *Concerta XL* (Janssen–Cilag) and *Medikinet Retard* (Medice) all provide a mixture of immediate- and extended-release methylphenidate; they differ in the physics of the delayed-release system and in the proportion of immediate to delayed. Figure 1 shows the pharmacokinetic (PK) profile over time of these different formulations; the actions on behaviour parallel the concentrations in the blood.

Concerta XL

Pharmacology: Concerta XL employs an osmotic pump system (OROS®), which has been designed to have a12-h duration of effect. An 18 mg tablet includes a shell of 4 mg immediate-release (i.e. 22%). In clinical trials, *Concerta XL* has been shown to be as effective as 3-times-a-day methylphenidate [48, 80]. However, a 20% higher dose of Concerta XL was required in the Pelham et al. [48] study.

MPH IR BID 	% IR	% ER	CONCERTA XL 	% IR	% ER
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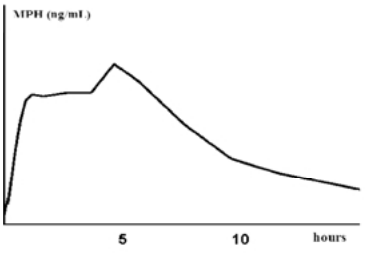
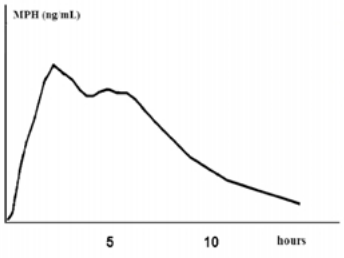
EQUASYM XL 			MEDIKINET RETARD 		
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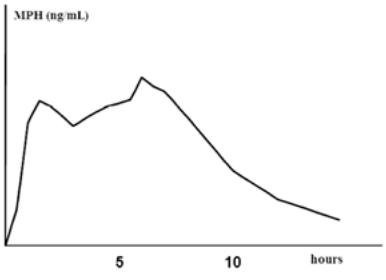
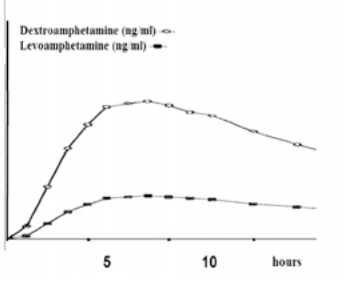
RITALIN LA 			ADDERALL XR 		
	50%	50%		50%	50%

Fig. 1 MPH and amphetamine plasma levels over time with different preparations and their IR/ER proportions Note: curves for MPH IR BID, *Medikinet retard* provided by Medice, for *Adderall XR* provided by Shire; for *Ritalin LA* see: Markowitz et al. [39]; for *Concerta XL* and *Equasym XL* see: Gonzalez et al. [21]; all curves are adapted to a common time-scale. Doses of different products are not equivalent so there is no common Y-axis and direct comparisons should not be made for the absolute levels

Time course of action: After oral administration of *Concerta XL* to adults, plasma methylphenidate concentrations rise and reach an initial maximum after 1–2 h, due to the capsule drug overcoat dissolving. Following this, the concentrations increase gradually, due to slow release from the capsule functioning as an osmotic pump designed to deliver MPH with an ascending profile for about 10 h after administration [69]. The action on behaviour is stated to last about 12 h [69]; but clinical experience suggests that (as with other ER preparations) there is considerable inter-individual variation.

Clinical aspects: Concerta XL is usually available in 18, 36 and 54 mg strengths. The tablets are administered orally once daily in the morning, must be swallowed whole with the aid of liquids, and must not be chewed, divided or crushed. *Concerta XL* may be administered with or without food. Dosage should be individualised according to the needs and responses of the patient, often by starting with 18 mg and adjusting in 18 mg increments at approximately weekly intervals. The maximum dose is stated as 54 mg; but this takes no account of the patient's size and the guidelines group consider higher doses up to

a maximum of 2 mg/kg/day; or 108 mg total daily dose—whichever is the smaller, to be acceptable and recommended in some cases. It is possible to titrate children straight on to *Concerta XL* without their needing to be first titrated on to immediate-release stimulant medication [68]. Some clinicians, however, prefer to establish the optimal dose by first titrating with immediate-release.

Equasym XL

Pharmacology: In *Equasym XL*, the capsules comprise both immediate- and extended-release beads such that 30% of the dose is provided by the immediate release component and 70% of the dose is provided by the extended-release component.

Time course of action: In line with its different dosing profiles, *Equasym XL* has a shorter duration of action than *Concerta XL* (approximately 8 h) but a larger effect in the 4–5 h immediately after dosing given similar total daily doses [70]. As with *Concerta XL* there is variation between individuals in the time course of action.

Clinical aspects: At the time of writing, *Equasym XL* is only available in the UK. The drug is administered once daily in the morning, before breakfast. Our recommended starting dose is 10 mg once daily. The company's advice is that dosage may be adjusted in weekly 20 mg increments to a maximum of 60 mg/day; our experience is in line with this, but there may be a limited number of cases who benefit from higher doses and the maximum for them is 2 mg/kg/day; or 100 mg total daily dose—whichever is the smaller.

Medikinet retard

Pharmacology: This is another proprietary formulation of methylphenidate, made in Germany and licensed only there at the time of writing, mixing 50% immediate with 50% extended, coated for gastric acid resistance.

Time course of action: The effective action is at least 7 h and the effects of once daily *Medikinet Retard* are comparable to the effects of twice daily Ritalin [11]. As with *Equasym XL* the dosing profile predicts a larger immediate, and smaller delayed, action than *Concerta XL*, with individual differences in time course being observed.

Clinical aspects: The drug is administered once daily in the morning, after breakfast. If titration is done with this drug our recommended starting dose is 10 mg once daily. The company's advice is that dosage may be adjusted in weekly 10 mg increments. The maximum dose is as for *Equasym XL* (above).

Ritalin LA

Pharmacology: Ritalin LA includes a mixture of immediate- and extended-release beads using the proprietary *SODAS* (Spheroidal Oral Drug Absorption System) drug delivery system. It has about 50–50 proportions of immediate and delayed release. It is licensed in a small number of European countries as well as the USA.

Time course of action: As with *Equasym XL* and *Medikinet Retard* the dosing profile predicts a larger immediate, and smaller delayed, action than *Concerta XL* and some evidence supports this [36].

Clinical aspects: Recommended doses are as for *Equasym XL*.

One characteristic of *Ritalin LA*, *Medikinet Retard* and *Equasym XL*, is that the capsules can be opened and the contents sprinkled on a suitable foodstuff without any loss of activity. In most cases, formulations are not licensed for this use and this practice is not recommended by the manufacturers. However, 'sprinkling' can be useful for children who have difficulties swallowing. It has also been suggested that given this characteristic these formulations could be easier to abuse, although there is no evidence for this view.

Adderall XR

Pharmacology: Adderall XR, like its IR predecessor Adderall, is composed of four amphetamine salts: amphetamine aspartate, amphetamine sulfate, dexamfetamine[1] saccharate, and dextroamfetamine sulfate (this last is the active ingredient of Dexedrine). These four component salts are metabolised at different rates. *Adderall XR* utilises a beaded delivery system in which the first type of bead dissolves immediately and the second type 4 h later. The drug is not licensed in Europe, but clinicians may encounter it in immigrants already using it.

Time course of action: Maximum plasma concentration is achieved in 7 h, compared to regular *Adderall IR* (immediate-release) that reaches maximum plasma concentration within 3 h. The duration of action is around 8–10 h [42].

Clinical aspects: Doses for both immediate- and extended-release form come in 5, 10, 15, 20, 25, and 30 mg increments.

[1]The spelling of dexamfetamine reflects the changes made in 'Recommended International Non-proprietary Names' (rINN) and 'New British Approved Names' (BAN) and follow European Directive 92/27/EEC. "Amphetamine" has not yet followed the convention. We are therefore following this inconsistent rule of spelling to help people using electronic retrieval. Trade rather than generic names of drugs have been used to distinguish the different preparations conveniently.

Two other extended-release stimulants, *Ritalin-SR and Focalin XR* (dexmethylphenidate extended release) will not be covered in this review. *Ritalin-SR* is likely to be replaced in the market by the more clinically effective *Ritalin LA*. *Focalin XR* is currently not available in Europe.

Adverse effects and misuse of stimulants

All stimulants, whether immediate- or extended-release, share some disadvantages. They can be both abused by the patient and diverted to an illegal recreational market. They, therefore, represent a potential public health risk. They are sometimes ineffective. The adverse effects (insomnia, appetite loss, growth retardation, abdominal pain, and occasionally dysphoria, tics or agitation) can sometimes be unacceptable. The issue of long-term growth retardation has received much attention recently but the issue is complex and current data are conflicting [70, 78] and do not allow the effects to be determined definitively. Nevertheless, the group recommend that children's height and weight should be monitored as a matter of course and followed on growth charts. Stimulants are contraindicated in several circumstances, most of them uncommon in childhood: schizophrenia, severe depression, hyperthyroidism, cardiac arrhythmias, moderate to severe hypertension, angina pectoris, glaucoma, previous hypersensitivity, or concomitant use—or use within the last 2 weeks—of monoamine oxidase (MAO) inhibitors. Caution is advised in: patients with motor tics, patients with known drug dependence or history of drug dependence or alcoholism, pregnancy and breast-feeding, anorexia nervosa, or a history of suicidal tendency. People with pre-existing cardiac abnormalities may be at special risk. Strategies for dealing with side effects include monitoring, dose adjustment of the stimulant, switching medication, and adjunctive pharmacotherapy to treat the side effects (see [71]).

Stimulants were introduced at a time when drug hazards were less rigorously monitored than is now the case. Strattera has been developed under stricter surveillance, and as a result some uncommon adverse events have been notified to regulatory authorities (see below). This in turn has led to a need to reconsider the possibility that stimulants too could have relationships with cardiac arrhythmias, liver failure, suicidal thoughts and seizures. For example, an unpublished report provided to a panel of the (US) Food and Drug Administration described seven reported cases of sudden death in children taking methylphenidate, relative to about 10 million prescriptions. In present knowledge, we think it is unlikely that this is greater than the rate in the untreated population, but also that the true figures of adverse reactions are probably greater than reported. The main practical implications are to include physical examination before prescription—to seek for cardiovascular abnormalities such as raised blood pressure or heart murmurs (ECG is optional) and enquire about symptoms such as syncope on exercise, with cardiological evaluation if a warning sign is found; and to include enquiry about seizures, signs of liver damage, or heart irregularities in monitoring patients. These recommendations are the same as those for immediate-release drugs, and do not differ for different stimulants or preparations. Routine blood tests are not recommended by us (though they are by the companies); blood dyscrasias can occur as a rare event, as with most medicines, but there is no suggestion either that the risk is big enough to justify monitoring or that it could be detected by infrequent tests.

Stimulants are controlled substances. Nevertheless, a meta-analysis of long-term naturalistic studies of stimulant treatment in ADHD concluded that stimulant treatment does not increase the risk of substance abuse [79].

Limited information is available regarding the inappropriate use of stimulants in patients with ADHD. Data on different forms of misuse (e.g., for cognitive enhancement by healthy people) and diversion of stimulants are few. Recently, Wilens et al. [77] evaluated the prevalence and correlates of stimulant diversion and inappropriate use in young North American adults with ADHD using a self-report questionnaire. It was based on a relatively small cross-sectional sample. They found, rather alarmingly, that out of 98 subjects with ADHD who were taking medication, 11% said that they had sold their prescribed medication, and 22% had "misused" medication in the sense of escalating dose without proper authorisation.

The 2004 US National Survey on Drug Use and Health also found evidence that a minority of patients may sell or misuse the medication [53] and a survey of 10,904 randomly selected college students in the US found that the life-time prevalence of non-medical prescription stimulant use was 6.9% [41]. Data for Europe are lacking. Little evidence was found of misuse/diversion in subjects with ADHD who did not already have substance abuse or conduct problems. All of the medications misused/diverted were immediate-release preparations of stimulants, suggesting that extended-release stimulants are less likely to be used inappropriately or diverted. This in turn suggests that IR formulations of MPH should not be prescribed in drug abusers and high-risk populations as first choice.

In some European countries, the perceived risk of drug abuse has led to stimulants being forbidden on public health grounds. We considered that this is a

disproportionate response, causing disadvantage to patients without likely impact on rates of substance abuse.

Non-stimulants

Atomoxetine hydrochloride—Strattera

Pharmacology: ATX, brand name *Strattera*, is a selective noradrenaline transporter blocker. It is currently licensed in several countries for the treatment of ADHD in children over six and adolescents and adults who were treated as adolescents. It is metabolised by the cytochrome enzyme P450 2D6; people with low levels of activity of this enzyme metabolise the drug more slowly and may well need lower doses. Drugs inhibiting P450 2D6 (such as fluoxetine)[2] will lead to higher blood levels of Strattera and may call for dosage adjustment.

Time course of action: The full effect of the medication appears only after 6–8 weeks of treatment or longer; but responders usually show some change by the 4-week point. Once full clinical effectiveness is established this appears to persist across the day at a fairly consistent level.

Clinical aspects: Like the stimulants, *Strattera* is indicated as an integral part of a multimodal treatment programme for patients with ADHD. *Strattera* is available in 10, 18, 25, 40, or 60 mg capsules (for oral administration with or without food). In children and adolescents up to 70 kg in body weight, *Strattera* should be initiated at a total daily dose of approximately 0.5 mg/kg and increased after a minimum of 7 days to a target daily dose of approximately 1.2 mg/kg administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. However, a single evening administration produces lower efficacy and less side effects [26]. The total daily dose in children and adolescents should not exceed 1.8 mg/kg or 100 mg, whichever is less.

Modanil—Provigil

Pharmacology: This is a chemically distinct drug, established for the promotion of wakefulness, with non-dopaminergic activating action on frontal cortex.

Time course of action: The effect is apparent from about 1 week of therapy.

Tablets are 100 mg. The dose is around 350 mg daily for children up to the age of 12.

[2]Useful websites with fuller information about these interactions can be found at http://medicine.iupui.edu/flockhart/table.htm or at http://www.medscape.com/druginfo/druginterchecker?src=ads

Clinical aspects: Modafinil does not (at the time of writing) have a marketing license for ADHD. The guidelines group does not have sufficient experience with it to make detailed recommendation, but it could potentially be considered for children refractory to other therapies.

Adverse effects of non-stimulants

A direct comparison of the adverse effects of *Strattera* and extended-release stimulants is not really possible on the basis of published data because Strattera has been introduced at a time of closer regulation and more explicit reporting; while stimulants have been used for much longer period with correspondingly greater chance of rare hazards appearing. For *Strattera* common adverse effects include nausea, sedation and appetite loss; other side effects of *Strattera* include dry mouth, insomnia, constipation, and mood swings. Additionally, urinary retention and sexual dysfunction have been observed in adult patients. Most of these adverse effects diminish over the first months of treatment. There is no significant difference in adverse events between normal and poor metabolisers of *Strattera*.

Regulatory agencies, such as the MHRA (Medicines and Health Care Products Regulatory Agency) in the UK, collect spontaneous reports about problems that have arisen in people treated with drugs. It can, however, be hard to know whether such problems would have arisen even if the drug had not been given. The most common serious events reported have been seizures: up to May 2005, there had been 212 recorded, from about 2.2 million treated, and the figure is likely to underestimate the rate. Many, however, were reported from people who were already prone to seizures, or were taking other drugs that can cause fits. The company reckoned that only 4 of the 212 events had no obvious cause other than *Strattera*, and so it is not clear whether the drug can cause seizures. We recommend caution: enquire about seizures before prescribing, monitor seizure frequency in those with epilepsy, and be alert to the possibility of seizures appearing for the first time.

Suicidal ideation appears rarely—0.44% of people treated in studies—but this is significantly more frequent than in those given placebo (0%) [4], so prescribers should be aware of this association and prepared to detect depression and suicidality and to treat, or refer, if necessary. Similar data for stimulants are currently lacking. For *Strattera*, irritability, agitation, anger or aggression may also occur in rare cases.

The warnings given for serious idiosyncratic hepatic events are similar to those for stimulants. *Strattera* therapy should be discontinued in patients

who present with signs or symptoms of liver injury such as jaundice, dark urine, or unexplained, persistent "flu-like" symptoms, and these should be asked about. Patients who develop symptoms of hepatic disease should discontinue *Strattera*. Chemical monitoring of hepatic function is, however, not recommended [51]. Blood pressure can be increased and should be monitored throughout therapy. The MHRA has received reports of QT interval prolongation—not enough to establish a link, but with particular concern after overdose. We do not think that there is a need for routine ECG monitoring, but recommend it for people already known to have long QTc intervals (or a family history), or who are also receiving drugs that can also produce QT prolongation, or cause electrolyte disturbances, or inhibit cytochrome P450 2D6.

Unlike stimulants, preliminary data on *Strattera* do not show any potential for abuse or long-term effects on growth [64]. The following side effects have been reported for *Modafinil*: insomnia, headache, nausea and anorexia as common adverse effects; skin rashes, including erythema multiforme and Steven-Johnson-syndrome as less common ones. It is contraindicated in hypertension and heart failure.

Costs of medications

Table 1 indicates the current prices of drugs for all available doses, based on those for the UK and Germany. These data should be seen only as a guide; the excess costs of extended-release over immediate-release may be less when other factors are taken into account, such as the costs of in-school dosing for short-acting medications given in school hours [38].

Recommendations for use of long-acting formulations

Should extended-release preparations be used?

The group was clear that there are benefits for at least some children from preparations that can be given once daily. They can be seen as superior to placebo and some are equivalent to multiple doses of immediate-release methylphenidate (see Part II for evidence for this and other recommendations; the guidelines group regard this as established at *Grade A* according to the SIGN system given in Appendix 1). The main countervailing argument is cost. This is certainly a consideration for all publicly funded services and some private practices. In reviewing the published literature, NICE found little difference in efficacy between multiple doses of immediate-release methylphenidate and single doses of long-acting formulations [30]. They also found no good evidence to establish difference in efficacy between extended release methylphenidate formulations and *Strattera* in terms of the reduction in core symptoms although this view is challenged by recent meta-analysis, supported by our review below, showing a significantly greater effect of stimulants [15]. This evidence should not be considered conclusive given limitations in the evidence base and dearth of well-designed head-to-head trials. The relative cost-effectiveness of the stimulants is, therefore, largely but not solely determined by the price of the drugs in the absence of good data on other indicators such as those relating to Quality of Life (QoL), while efficacy may become an issue when non-stimulants are considered. In current practice, dexamfetamine is substantially the least expensive; but in our view this would not be preferred

Table 1 Indicative annual cost of licensed drugs (February 2006)

Generic	Proprietary	UK cost per tablet per year (British National Formulary)	Germany[a] cost per tablet per year (Net wholesale price including tax)
Methylphenidate hydrochloride	Equasym	30 mgm/day = 273 €	30 mgm/day[a] = 390 €
	Ritalin	30 mgm/day = 345 €	30 mgm/day = 577 €
	Medikinet	Not available	30 mgm/day[a] = 390 €
	Concerta XL	36 mgm/day = 666 €	36 mgm/day = 1.072 €
	Equasym XL	30 mgm/day = 867 €	Not available
	Medikinet retard	Not available	30 mgm/day = 897 €
Dexamfetamine sulphate	Dexedrine	15 mgm/day = 113 €	Not available
Atomoxetine	Strattera	Once daily = 1.068 €	Once daily[b] = 1.286 €
		Twice daily = 2.136 €	Twice daily[c] = 2.634–2695 €

Costs based on UK and German prices. Ritalin LA, which is not available in either country, costs 447 € per tablet per year in Belgium

[a] German prices for Equasym and Medikinet are based upon 20 mg tablets, for Ritalin on 10 mg tablets (20 mg not available). Corresponding prices for 10 mg tablets Equasym or Medikinet are 514 €

[b] 40 or 60 mgm/day

[c] Depending on dose

NB prices vary from time to time, do not include costs of monitoring and cotherapies, and are not the major decision in prescribing. The doses cited are not necessarily equipotent

over MPH because of its perceived presence in the illegal drug scene and by the lack of good evidence on safety (*Good Practice*). This aspect needs further study. Excluding dexamfetamine, the next most cost-effective is immediate-release methylphenidate. The guidelines group recommend this as the drug of first choice for the majority of patients when cost is a consideration. The extra cost of extended-release is hard to give precisely; it depends on pricing policies in different countries that may change from time to time. NICE economists attempted a calculation of the cost for units of gain in the QoL of patients being treated with *Concerta XL, Equasym XL* and *Strattera* [30]. In general, the costs for available treatments fall within the range that European society accepts in medical treatment, and correspondingly all three drugs types should be available in treatment regimes. Calculations such as this do not give guidance for the clinician in the individual case. For one thing, they are heavily dependent upon very questionable estimates about both the number of children who will fail to comply with a regime and the changes achieved in QoL measures.

Drugs with longer action have other advantages, which may vary as a function of the administrative context in different EU countries—especially, that they do not have to be taken at school. The school does not have the expense and risk of maintaining good administration, and the child does not have the potential stigma of being seen to take a pill. Compliance may be correspondingly better, but data are few. ADHD patients on long-acting preparations may be more likely to persist on their medication than those prescribed IR MPH and have significantly fewer emergency room visits and general practitioner visits per patient, on average, over 1 year [28, 34]. An individual decision therefore needs to be made in the light of the child's circumstances. A little evidence (*Grade C)* suggests that sustained release medications may be less prone to abuse because they tend to have a slower rate of onset of effect than IR medications [73]. Kollins et al. [32] assessed the effects of sustained-release methylphenidate (SR—equivalent to extended release), immediate-release methylphenidate (IR), and placebo among ten healthy volunteers. The IR medication produced increased ratings of pleasant effects. In contrast, the SR formulation produced only transient effects. These results should be taken with caution until good data emerge on abuse potential. In summary, the guidelines group consider the key advantages of immediate-release stimulants to be its lower cost and flexibility of dosage; the key advantages of long-acting drugs as a potential reduction of stigma at school, and improved compliance and possibly reduced risk of misuse. The conclusions were therefore (1) that long-acting preparations should be available and used; and (2) that they should not entirely replace short-acting drugs. Individual clinical choice will determine the choice of formulation used.

Which long-acting drug to use?

The comparative merits of the long-acting preparations have been hotly disputed. Part 3 of this paper provides a detailed review. Although between-study comparisons of effect sizes are useful, they must be considered cautiously because the trials being compared differed not only in the type of active medication employed but also in other design features that may have affected the results (e.g., outcome measures, raters, doses, experimental design). There are some trial data based on direct comparisons of *Concerta XL* and the other drugs. These include data against *Equasym XL* [70] and *Strattera* [76]: The first highlighting the different profile of effect across the day and the second suggesting that *Concerta XL* had a significantly larger effect. This latter trial did, however, exclude children who previously had a poor response to methylphenidate. This was for sound ethical reasons—it would scarcely have been justifiable to randomise them to a drug known not to help them. But the effect could well have been to bias the comparison in *Concerta XL*'s favour; and a subgroup analysis of children who had not previously received stimulants (the key group for clinicians choosing the first treatment) yielded no significant differences between the preparations. A recent comparison of *Adderall XR* and *Strattera* suggested that the mixed amphetamine salts of *Adderall XR* had, in the doses administered, the larger effect on a hyperactivity rating scale [76]. In line with meta-analysis [15], the review reported here suggests that the effectiveness of *Strattera* is likely to be somewhat less than that of stimulants generally, on the basis of the data provided by the companies—but the studies are heterogeneous in design, doses and subjects treated. In terms of normalisation rates and numbers needed to treat, differences are less obvious. Qualitative as well as quantitative considerations, therefore, come into the choice of a long-acting preparation. For instance, *Strattera* can have an action throughout the day and this may be welcome to families who may struggle in mornings and evenings [27]. It helps some children who are not helped by methylphenidate (and vice versa).

The balance of adverse effects is different for stimulants and non-stimulants—*Strattera* is more likely to produce somnolence, methylphenidate insomnia; *Strattera* nausea, methylphenidate anorexia. *Strattera* may, therefore, be particularly useful when adverse effects have limited the value of a stimulant. There is possibly a lower abuse potential

for *Concerta XL* related to properties inherent in the OROS technology compared to other MPH-ER formulations (although further research is needed to test this, see above)[3] However, *Strattera* may be considered as a first choice in populations at risk. It does not have a greater abuse potential than desipramine [24].

Both *Strattera* and extended-release preparations of methylphenidate should be available. *Adderall XR* has not been considered in detail in this guideline because of its unlicensed status in Europe. The choice will depend upon the circumstances:

If treatment is starting with a long-acting preparation, then considerations[4] of the anticipated average cost/dose and efficacy suggest starting with extended-release methylphenidate and proceeding to *Strattera* if the former is unhelpful (*Grade B for comparative effect)*. The choice of extended-release methylphenidate will depend upon the profile of action required over time, and upon the availability of drug. *Strattera* is a relatively expensive drug; so a cost-effective policy will usually reserve it for cases where methylphenidate is unhelpful or contraindicated. It may nevertheless be preferred as first choice if substance abuse or comorbid tics are a problem, if there is a strong family preference for a non-stimulant, or if a 24-h action is particularly strongly required [27].

If a child has responded well to immediate-release methylphenidate, there may still be reasons to shift to extended-release—for example, to avoid the stigma or inconvenience of repeated dosing. Clearly, an extended-release preparation of methylphenidate will then be preferred.

If a child has suffered adverse effects on immediate-release methylphenidate, then the next step will often be to proceed to *Strattera* (*Grade B* for difference in adverse effect profile; see above). The previous 'European Guidelines' paper outlines symptomatic actions to be taken to limit the impact of adverse effects [71]. For instance, growth effects are not sufficiently different between drugs that one rather than another should routinely be preferred on those grounds. But, if an individual child's growth is decelerating on stimulants and cannot be managed conservatively then a switch to *Strattera* is a rational move.

If a child has failed to respond to immediate-release methylphenidate because of lack of efficacy rather than adverse effect, then the next option to try either immediate release dexamfetamine if available and acceptable (see above and previous guidelines [71] or *Strattera*). If dexamfetamine fails, or is unacceptable or unavailable, or if the presence of substance misuse, or family choice, contraindicates dexamfetamine, then *Strattera* should be considered. *Grade B* evidence suggests that methylphenidate non-responders have around a 40% chance of responding to *Strattera* [43].

Which extended-release preparation of methylphenidate?

Clinical practice will often begin with a decision about profile of effect desired across the day. Loss of control in the evenings or preference for evening control by the family will indicate the longer acting; insomnia may suggest the shorter-acting one. The smaller initial effect of *Concerta XL* may mean that morning control is achieved at the price of greater overall exposure to methylphenidate compared to *Equasym XL*, *Ritalin LA* or *Medikinet Retard*. Where this is an issue (e.g., for the family) then *Equasym XL*, *Ritalin LA* or *Medikinet Retard* would be preferred. An alternative strategy would be to combine *Concerta XL* with a morning dose of immediate release (see below). There is, however, a range of individual variation. *Equasym XL* is somewhat more expensive (at the time of writing) but has the property, along with *Medikinet Retard* and *Ritalin LA*, that the capsules can be opened and the contents sprinkled on food. This helps some children who have difficulty swallowing; but the opportunity to administer it surreptitiously should not be taken because of the potentially harmful effects of stealth on trust.

Should combination of treatments be used?

Extended-release preparations were designed to give a good profile of action across the day. Nevertheless, the range of individual variation suggests that some children on extended-release formulations may be helped by an additional dose of immediate-release (beginning with 5 mg); either in the morning to assist with control at the beginning of the day; or in the evening to prevent an unsettling loss of action (which may manifest either in disruptive behaviour or in initial insomnia).

Other considerations

Comorbidity

Little evidence exists of the specific advantages or disadvantages of short-acting versus long-acting treatments in relation comorbidities. In general, more

[3]However, the IR MPH overcoat of the capsule could still be misused.

[4]Since these are determined by price, and price will vary from time to time and place to place, the prescriber is advised to check these generalisations against current circumstances. When considering the total medication costs there is more than just the cost of one pill to consider. Many patients taking one medication require longer coverage, top-up doses and medication for comorbidities or side effects. One should not choose a long-acting medication purely based on price.

RCT data is available for Strattera than other formulations.

Tics: Methylphenidate is not necessarily contraindicated in people with tics although in individual cases it can be a hazard [47, 72]. Responsive discussion with the family is useful to determine the utilities they attach to tic severity against severity of ADHD. In the case of treatment-emergent tics or comorbid tics *Strattera* is a useful alternative and does not worsen tics and may even improve them [2].

Anxiety: Patients with ADHD and comorbid anxiety or disruptive behaviour disorders have as robust a response of their ADHD symptoms to stimulants as do patients who do not have these comorbid conditions [45]. A 12-week double-blind, placebo-controlled trial [67] found that *Strattera* significantly reduced symptoms of both ADHD and anxiety relative to placebo, showing the drug to be efficacious in the treatment of both conditions with a moderate effect size (0.5) for anxiety.

Oppositional defiant disorder: A meta-analysis of 28 studies found that stimulant effects for aggression-related behaviours in ADHD had effect sizes similar to those for the core symptoms of ADHD but these effects were smaller for patients diagnosed with conduct disorder [9]. Extended release methylphenidate formulations [63, 74, 80], *Adderall XR* [62] and *Strattera* [25, 46] have been shown to be effective at treating comorbid cases. Data for *Strattera* are conflicting with regard to effects on symptoms of ODD themselves, with an effect-size of 0.39 in the US-study [46] and a lack of significance in a European study [3].

Depression: Preliminary data suggest no effect of *Strattera* on depression (unlike stimulants for which it is a recognised though uncommon complication). *Strattera* should not be regarded as an anti-depressant.

Autism or mental retardation: Both stimulants and Risperidone can be superior to placebo in treating hyperactivity/impulsivity when it occurs in people with Autism or mental retardation. Risperidone has not been considered elsewhere in these guidelines, as it is not approved generally for the treatment of ADHD, but it may well be considered if autism is present too. Pending further research, these combinations of symptoms are not a specific indication for either ER stimulants or Strattera. Due to the potential for increased side effects cautious dosing for these combinations of symptoms is required.

ADHD across the lifespan

Pre-school ADHD: The diagnosis of pre-school ADHD is deemed problematic by many clinicians but can be made reliable [58]. This is despite persisting concerns over the difficulty of distinguishing ADHD from normal developmental variations in activity and attention [59]. Given concerns about the lack of evidence relating to the long-term effects of very early initiated extended MPH treatment, drugs should be prescribed very cautiously and evidence-based psychological approaches (such as structured parent training) should normally take precedence in the first instance. Evidence with regard to the efficacy of short acting MPH formulations was described in the revised European guidelines [71]. While MPH can be efficacious for pre-schoolers, RCT evidence is sparse and where available effects on core symptoms were generally smaller and side effects more pronounced than for older children [22, 33]. There is currently no evidence, (and no evidence was submitted to the Guidelines group) specifically in relation to the efficacy of effectiveness of long-acting stimulant or non-stimulant drug formulations in pre-school ADHD.

Adult ADHD: ADHD often persists beyond the adolescent years, with the majority of cases displaying either the operationally defined disorder or the persistence of some symptoms associated with significant levels of academic, occupational and social impairment and a high level of psychiatric comorbidity [5, 13, 16, 19, 50]. Clinical experience suggests that there is a significant subset of individuals who benefit greatly from the appropriate use of stimulants and other drug treatments, but data do not allow accurate estimation of the proportion of individuals with ADHD who require long-term medical treatment. At the time of writing, most drug treatments are not licensed for use within the adult population in any European country. This means that current prescriptions are written 'off-label'. The exception is *Strattera*, which is licensed for use in adults but only when treatment was initiated in childhood or adolescence. Nevertheless, the guidelines group conclude that both stimulants and Strattera are effective in adults with ADHD and recommend their clinical use, both for individuals who started treatment in childhood/adolescence, as well as for individuals receiving a first time diagnosis of ADHD in adulthood.

In most cases, lack of licensing in the adult population has not come about from failed licensing applications, but rather from a historical lack of interest of treating ADHD in adults from both clinicians and drug companies. It is envisaged that this situation will change in the near future since several of the ER preparations are undergoing European trials in adult ADHD samples to demonstrate the safety and efficacy levels required by the licensing agencies. The treatment of adults is likely to remain a specialist interest in the short-

term, although in the medium term an increasing number of adult psychiatrists and adult mental health services are expected to incorporate treatment of ADHD into their general practice.

The short-term effectiveness of stimulants in adult life has been demonstrated with meta-analysis of available data showing similar effect sizes to that seen in child and adolescent samples [17]. They concluded that the degree of efficacy of MPH, in treating adults with ADHD, was similar to that reported from meta-analyses of the child and adolescent literature, providing assurance for clinicians that the diagnosis and treatment of ADHD can be validly applied in adulthood. The one area where different parameters may operate is dosage level. Titration to an effective dose is important [17]. The most common dose range used in European adult ADHD clinics for IR methylphenidate is 10–20 mg taken 3–5 times daily, with both higher and lower dosing required in individual cases. Our suggested maximum is 30 mg for each dose. The use of extended release stimulants has been less extensively investigated in the adult ADHD population but the similarity in treatment effect sizes for IR MPH suggests that the guidelines for their use in older children and adolescents should be followed for adults. As with IR preparations titration to a clinically effective dose is required. One large trial of *Concerta XL* [6] involved a randomised, 6-week, placebo-controlled, parallel design study of *Concerta XL* in 103 adult patients with DSM-IV ADHD. Dosage could be titrated up to 1.3 mg/kg/day; the average daily dose used in this study was 72 mg, and the maximum 108 mg/day.

For an adult with a long working day and responsibilities in the evening, or where marked behavioural symptoms such as irritability and impulsivity appear once the effects of medication wear off alternative treatment may be needed. Careful consideration of the timing of reappearance of symptoms and the PK profile of each drug should be considered in deciding whether to opt for a supplement of IR medication or a change to Strattera (see below). Similar treatment effect sizes to those seen in children have also been shown within available drug trials of *Strattera* [1, 44, 56]. As in children the possible advantages include reduced potential for drug misuse, extended action throughout the day and a different profile of side effects and hazards. The usual daily dose for adults is 100 mg taken once per day. The same arguments for and against the use of extended release preparations in children and adolescents also apply to adults. The main difference here is the way that the treatment options are evaluated since adult patients are often capable of providing detailed descriptions of their personal preferences. The main indications for choosing ER preparations include compliance issues, stigma or inconvenience in the work setting, individual differences in response to drugs with different PK profiles, and concern over potential drug misuse. Depending on the profile of symptoms and associated impairments, individuals often express preferences—either for drugs that have sustained effects, such as *Strattera* or ER preparations, or for IR preparations, which provide flexibility for some individuals who do not require or desire treatment all the time. Some individuals have trouble with the on-off effects of IR drugs and prefer the 'smoother' effects of ER preparations. Others have no trouble regulating their use of IR medication and prefer the added control that use of IR preparations gives them for dose and timing of dose throughout the day. The choice of drugs with different PK profiles increases the chances of finding one that is suited to an individual patient's symptom profile and individual clinical requirements.

A quantitative comparison of long-acting treatments

Pharmacokinetics

Laboratory studies suggest a close relationship between PK and pharmacodynamic (PD) properties; PD studies of both IR & ER stimulants suggest that the PD profiles closely mirrors both the IR & ER PK profiles. Thus, methylphenidate plasma levels of different ER-stimulant preparations measured over time across the day correspond to their profile of efficacy [21]. Clinical superiority at any point in time is typically achieved by the formulation with the highest expected plasma MPH concentration [60, 70]. Thus, when given in roughly equivalent daily doses the relative efficacy of preparations with different dose delivery and PK profiles will vary depending on the time since dosing. For example, *Equasym XL* was found to be more effective than *Concerta XL* early in day and vice versa late in day [60, 70]. Figure 1 illustrates the typical plasma level profiles for stimulants considered in this review over time as a function of each formulations relative IR and ER proportions. Bioavailability curves for MPH IR BID and *Medikinet retard* were provided by Medice and for *Adderall XR* by Shire; the curve for *Ritalin LA* is based upon Markowitz et al. [39]; curves for *Concerta XL* and *Equasym XL* are based upon Gonzalez et al. [21]. All bioavailability curves were adapted to a common time scale (X-axis: hours) by the authors and serve as a comparison of the relative bioavailability of the formulations over time, but direct comparisons

Table 2 Mean medication effect sizes (SMDs) on total ADHD symptoms by preparation and type of rater

	Parent		Teacher		Clinician		
Total ADHD	SMD	Number of studies (rating scales used)	SMD	Number of studies (rating scales used)	SMD	Number of studies (rating scales used)	References
Adderall XR	0.9[a]*	1	1.1[b]*	1	1.2[c]**	1	Data on file Shire
Concerta XL	1.0[d]	1	1.0[d]	1			Wolraich et al. [80]
Equasym XL	0.6[f]	2	0.9[d,f]	1	1.8[e]***	1	Greenhill et al. [23], Swanson et al. [70], Findling et al. [18]
Medikinet retard	1.0[g]	1	1.0[g]	1	0.9[e,c]***	1	Döpfner et al. [10, 11]
Ritalin LA			1.0[h]	1			Biederman et al. [7]
ATX	0.7[i]	6			0.7[c]	11	Data on file Eli Lilly
Modafinil	0.6[c]	3	0.7[c]	3			Data on file Cephalon

Rating Scales: [a] Conners' Global Index Scale-Parent Version (CGIS-P) (10 item); [b] Conners' Global Index Scale-Teacher Version (CGIS-T)(10 item); [c] ADHD-Rating Scale; [d] Inattention/Overactivity with Aggression (IOWA) Conners Scale; [e] Swanson, Kotkin, Alger, M-Flynn and Pelham (SKAMP) Scale; [f] Swanson, Nolan And Pelham (SNAP) IV Questionnaire; [g] Fremdbeurteilungsbogen-HKS (German version of the ADHD-Rating Scale); [h] Conners' ADHD/DSM-IV Scale—Teacher Version (CADS-T) (27 item); [i] Revised Conners' Parent Rating Scale (27 item)
*Only children studied
**Only adolescents studied; a non-linear dose-response relationship between dose and response was observed (20 mg: 1.2, 30 mg: 0.9, 40 mg: 0.9)
***Lab-school study

between the different preparations should not be made for absolute plasma levels (Y-axis) as these levels are dose-dependent. Moreover, it should be noted that PK profiles may show considerable inter-individual variation [29]. Caution should be observed when generalising from these aggregated profiles to individual patient cases.

Whilst these different delivery profiles do not distinguish any one preparation as "better" than the other, they do provide the clinician with increased options when choosing which preparation to use for a particular patient. They also allow clinicians to provide a more flexible and sensitive individualised adjustment whilst retaining the benefits of an ER preparation. In much the same way as it is possible to adjust individual doses of IR MPH to ensure that symptoms are adequately treated across the day, it is now also possible to choose an ER preparation whose PK, and thus PD, profile, matches the patients' needs and preferences.

Review methodology: rationale and procedure

Ideally, estimates of the relative efficacy of the different long-acting formulations would be based upon published high quality head-to-head comparisons. However, such direct comparative studies are largely lacking and those available rarely allow to firm conclusions about the comparative efficacy of the products to be drawn (e.g., because of exclusion of prior MPH-responders or too short study duration). Therefore, the group decided to compare the various efficacy measures of the different available products across studies, by using a common set of standard efficacy indices: treatment effect sizes (a measure of change) and numbers needed to treat (a measure of outcome) (see below). A working group (TB, DC, SP, AZ) made a systematic review of published clinical trial literature for the extended release preparations and unpublished clinical trial data provided by the companies. The review only included randomised, double-blind, placebo-controlled studies not excluding medication non-responder a priori and presenting the means and standard deviations of either change scores or endpoint scores for both medication and placebo groups.

A comparison of treatment effect sizes

The calculation of effect sizes standardises the magnitude of the difference between outcomes in drug and placebo groups so that a 1-point difference indicates that the active treatment and placebo groups differ by 1 standard deviation on a particular outcome measure. This allows a direct comparison of treatment effectiveness across studies. A commonly used effect size index is the standardised mean difference (SMD)—the difference in outcome scores between drug and placebo groups divided by the pooled standard deviation (of the placebo and medication group at end of treatment). Ideally, different medications should be compared by calculating the SMDs based on the same outcome score and the same type of rater for each medication. However, study design parameters, outcome measures and the type of rater often varied among the double-blind, placebo-controlled studies identified for review. Comparing effect sizes between studies is questionable if the studies differ substantially in design features that might influence medication versus placebo differences (e.g.,

Table 3 Mean medication effect sizes (SMDs) on inattention symptoms by preparation and type of rater (n = number of studies)

	Parent		Teacher		Clinician		
Inattention	SMD	Number of studies (rating scales used)	SMD	Number of studies (rating scales used)	SMD	Number of studies (rating scales used)	References
Adderall XR					1.2[a]*	1	Data on file Shire
Concerta XL			No data available				
Equasym XL	0.7[d]	2	0.8[b,d]	1			Greenhill et al. [23], Swanson et al. [70], Findling et al. [18]
Medikinet retard	1.0[e]	1	1.1[e]	1	0.8[c]**	1	Döpfner et al. [10, 11]
Ritalin LA			0.9[f]	1			Biederman et al. [7]
ATX					0.6[a]	10	Data on file Eli Lilly
Modafinil	0.6[a]	3	0.6[a]	3			Data on file Cephalon

Rating Scales: [a] ADHD-Rating Scale; [b] Inattention/Overactivity with Aggression (IOWA) Conners Scale; [c] Swanson, Kotkin, Alger, M-Flynn and Pelham (SKAMP) Scale; [d] Swanson, Nolan And Pelham (SNAP) IV Questionnaire; [e] Fremdbeurteilungsbogen-HKS (German version of the ADHD-Rating Scale); [f] Conners' ADHD/DSM-IV Scale—Teacher Version (CADS-T) (27 item)
*Only adolescents studied; SMD at 40 mg was 1.8
**Lab-school study

Table 4 Mean medication effect sizes (SMDs) on hyperactivity/impulsivity symptoms by preparation and type of rater (n = number of studies)

	Parent		Teacher		Clinician		
Hyperactivity/Impulsivity	SMD	Number of studies (rating scales used)	SMD	Number of studies (rating scales used)	SMD	Number of studies (rating scales used)	References
Adderall XR					1.1[a]*	1	Data on file Shire
Concerta XL			No data available				
Equasym XL	0.6[d]	2	0.9[b,d]	1			Greenhill et al. [23], Swanson et al. [70], Findling et al. [18]
Medikinet retard	1.0[e]	1	1.1[e]	1	0.7[c]**	1	Döpfner et al. [10, 11]
Ritalin LA			0.9[f]	1			Biederman et al. [7]
ATX					0.6[a]	10	Data on file Eli Lilly
Modafinil	0.5[a]	3	0.6[a]	3			Data on file Cephalon

Rating Scales: [a] ADHD-Rating Scale; [b] Inattention/Overactivity with Aggression (IOWA) Conners Scale; [c] Swanson, Kotkin, Alger, M-Flynn and Pelham (SKAMP) Scale; [d] Swanson, Nolan And Pelham (SNAP) IV Questionnaire; [e] Fremdbeurteilungsbogen-HKS (German version of the ADHD-Rating Scale); [f] Conners' ADHD/DSM-IV Scale—Teacher Version (CADS-T) (27 item)
*Only adolescents studied
**Lab-school study

different types of rater, durations of studies, dosing regimens). Therefore, SMDs for the various ER medications were calculated separately for different types of rater (parent, teacher, and clinician) and for the following outcome measures: total ADHD symptoms, inattentive symptoms, and hyperactive/impulsive symptoms. This approach was designed to help control for potentially confounding factors across studies.

If a study presented data on more than one fixed dose, the most efficient dose (which was usually the highest dose) to reduce total ADHD symptoms was used for the calculation of SMDs. As an exception, a non-linear dose-response relationship between dose and response (SMD) was observed for Adderall XR efficacy in the clinicians' ratings of total ADHD adolescents (20 mg: 1.2, 30 mg: 0.9, 40 mg: 0.9). Where there was more than one study dataset available, SMDs were averaged to a corresponding overall SMD. Averaging was done by weighting the single studies' SMDs by the corresponding numbers of subjects included in the study. Company calculations using a standard approach were employed for *Medikinet Retard, Strattera, Adderall XR, Modafinil*. The authors calculated the SMDs for *Concerta XL* based upon the results of a randomised, double-blind placebo-controlled study from a published paper [80]; two other randomised, double-blind placebo-controlled studies on *Concerta XL* were identified by the systematic review [48, 69]; these included MPH-responders exclusively (i.e., children who previously had a prior poor response to MPH were excluded) and their SMDs were substantially higher than those of studies investigating unselected samples. In order to ensure comparability, results

from these studies were not considered for the calculation of the SMDs for *Concerta XL*. SMD calculations for *Equasym XL* are based upon randomised placebo controlled studies provided by UCB [18, 23, 70].

Tables 2–4 give mean effect sizes (SMDs) for each preparation by the type of rater on ADHD symptom domains and the numbers of studies and rating scales (indexed) on which these figures are based upon. While the various long-acting stimulants differ according to their PK and PD profiles (see above), their SMDs are strikingly similar and comparable to the figures reported across raters for this class of medication in the recent meta-analysis; no significant difference in effect size was observed for immediate-release stimulants compared with long-acting stimulants [14, 15]. SMDs of immediate release methylphenidate on core symptoms of ADHD in children from randomised, double-blind, placebo-controlled trials are between 0.8 to 1 [14, 15, 30]; SMDs vary among symptom domains, with the strongest effects of stimulant medication on measures of attention, distractibility, and impulsivity and observable social and classroom behaviour. For adult ADHD, Faraone et al. [17] calculated a mean SMD of 0.9 based on six trials including a total of 140 MPH-treated ADHD adults and 113 placebo-treated ADHD adults. When treatment was optimised to high doses, the SMD for MPH in adults was 1.3.

Overall, our results support conclusions of the recent meta-analysis that long-acting stimulants have similar SMDs to immediate-release stimulants (*evidence level Ia*) while SMDs for non-stimulants are somewhat smaller [14, 15] Although it should be borne in mind that effect sizes cannot provide definitive guidelines for clinical practice, they do provide additional information for clinicians to consider when planning treatment regimens for ADHD patients [12, 14, 15]. Limitations of these data include the inability to control for the effects of potential confounding variables (differences concerning the distribution of diagnostic subtypes, gender, and age, design of study (parallel versus crossover; lab-school versus naturalistic setting), type of outcome score used (change score versus endpoint score), source of information of the clinicians' rating,[5] dosing method (fixed dose versus best dose), and use of placebo lead-in (yes/no).

A comparison of normalisation rates and numbers needed to treat

Normalisation rates are defined as the proportion of patients normalised, e.g., having no problems more than "mild" (i.e. Conners scale *T*-score < 63 or SNAP < 1/item). Once again these were provided by the companies, except for Concerta XL, for which no formal "Normalisation" analysis had been completed. The only published paper reporting normalisation data was Stein et al. [66], which was not an adequate double-blind study (appearance of placebo and OROS different). Thus, these figures cannot be compared to those of the other preparations. From these normalisation data, Number Needed to Treat (NNT) can be calculated (see below). The NNT corresponds to the expected number of patients needed to be treated to see one patient normalise in terms of ADHD symptoms with medication and would not have normalised on placebo therapy. This is a common treatment efficacy outcome measure in contrast to SMD, which is a measure of change by treatment. NNT is computed as follows:

$$\mathrm{NNT} = 1/(\text{Percent improved on Drug} - \text{Percent improved on Placebo} \times 100)$$

Confidence intervals (CI) for NNT are calculated as follows:

$$\mathrm{CI} = \pm 1.96 \times \text{Square root}[\{(\text{normalisation rate}^*(1 - \text{normalisation rate}))/\text{n placebo}\} + \{(\text{normalisation rate}^*(1 - \text{normalisation rate}))\text{n treated group}\}]$$

Whilst comparisons are somewhat limited by the use of different measures and slightly different definitions of normalisation (e.g., SNAP scores ≤ 1/item versus ADHS-RS ≤ *T*-score 63), figures suggest that differences between the ER medications investigated are smaller using this metric than using the SMD analysis. An exception is the data for *Concerta XL*. However, these normalisation data may be inflated because of an inadequate study design [66][6] and results should therefore not be compared directly to the other products' figures straightforward. The relative efficacy for *Strattera* using this index also seems stronger. One possible explanation for the discrepancy between measures may relate to a relatively larger efficacy of

[5]It has to be mentioned that clinician ratings were based on different sources of information. The *Medikinet retard* and *Equasym XL* studies used direct observations (lab-school ratings). In the *Strattera* trials, clinical investigators were specifically instructed not to use any other information as the basis for the rating except parent interviews (most *Strattera* studies), respectively teacher reports (one *Strattera* study;75. Weiss M, Tannock R, Kratochvil C, Dunn D, Velez-Borras J, Thomason C, Tamura R, Kelsey D, Stevens L, Allen AJ (2005) A randomised, placebo-controlled study of once-daily ATX in the school setting in children with ADHD. J Am Acad Child Adolesc Psychiatry 44:647–655).

[6]The appearance of placebo and Concerta XL was different, i.e. it was not a blinded study.

ER stimulants than *Strattera* on more severely impaired patients (which are not normalised by treatment). This possibility needs to be investigated further. (Table 5)

It is worth noting that the effect sizes and NNTs for these medications compare favourably with those reported for other psychiatric drugs. For example, the effect sizes and NNT for antidepressants in the treatment of adult depression or obsessive-compulsive disorder are in the region of 0.5 and 9, respectively [20, 61]; and for atypical antipsychotics in the treatment of schizophrenia are around 0.25 and 20 [35].

Quality of life

Quality of Life measurement is a desirable part of clinical trials, but has not often been applied sufficiently frequently, or has been applied with too little power [8]. Panels of parents have been asked to develop utility measures for cost-effectiveness estimates, but the method has not yet been able to give robust comparisons of drugs [30]. A systematic review is therefore not included in this paper. The Child Health Questionnaire is sensitive to the psychosocial deficits in ADHD [31] and was used to conclude that *Strattera* is superior to placebo in random-allocation double-blind trials ($n = 747$) [40, 49]. Open label studies of Strattera with a total of 921 participants [52] suggest an SMD of around 1.0 SD.—especially on a psychosocial summary score, a family activities subscale and a parent emotional impact subscale. The QoL Enjoyment and Satisfaction Questionnaire (Q-LES-Q) was used in a long-term open extension study of Adderall XR; parents rated a 15% increase after 1 year on treatment [37]. A range of specific domains of functioning that are likely to be related to QoL have been used to show positive effects of extended-release methylphenidate *Concerta XL*. These include family functioning, parental stress, social interactions, academic functioning/homework improvement [48, 65, 69].

Recommendations for future study

The database remains rather limited for all issues other than the comparison of drugs with placebo on symptom rating scales. The effects on QoL or utility ratings; the head-to-head comparisons between drugs; efficacy in subtypes of ADHD (such as hyperkinetic disorder and various comorbidities); effectiveness studies in real-world settings; and economic analyses such as cost-effectiveness; all need development. Long-term safety assessments are pressingly needed.

Table 5 Normalisation rates and numbers needed to treat by preparation and type of rater (95% CI for NNT)

Normalisation and Numbers needed to treat versus Placebo	Parent			Parent and teacher			Teacher			Clinician (Parent)[a]			Clinician (Teacher)[1]		
	% normalised active med	% normalised placebo	Number needed to treat (95% CI)	% normalised active med	% normalised placebo	Number needed to treat (95% CI)	% normalised active med	% normalised placebo	Number needed to treat (95% CI)	% normalised active med	% normalised placebo	Number needed to treat (95% CI)	% normalised active med	% normalised placebo	Number needed to treat (95% CI)
MPH IR[b]	41	20	4.8 (±0.15)	64	29	2.9 (±0.16)									
Adderall XR[c]	51	25	3.8 (±0.14)				54	36	5.6 (±0.15)						
Concerta XL[d]	*66*[d]	*14*[d]	*1.9*[d] *(±0.20)*												
Equasym XL[b]	39	20	5.3 (±0.15)	58	29	3.5 (±0.16)									
Medikinet retard[e]	49	12	2.7 (±0.18)				72	26	2.2 (±0.19)						
Ritalin LA	No data available														
ATX[f]	42.3	18.5	4.2 (±0.07)							45.5	22.5	4.4 (±0.05)	69.1	42.9	3.8 (±0.21)
Modafinil	No data available														

[a] Clinician ratings based solely on parent, respectively teacher reports; clinical investigators were specifically instructed not to use any other information
[b] Findling et al. [18]: average parent & teacher SNAP IV scores ≤ 1/item
[c] Spencer et al. [63]: SNAP mean scores ≤ 1/item
[d] Stein et al. [66]: ADHD RS-IV mean score ≤ 1/item; (54 mg Concerta XL versus placebo); appearance of placebo and Concerta XL was different, i.e. not a blinded study, thus the difference between placebo and OROS normalisation may be inflated; therefore, these figures may not be directly comparable to the other product's data
[e] Döpfner et al. [10]; Sinzig et al. [57]: FBB-HKS mean score ≤ 1/item
[f] Lilly provided table for normalisation rates based on all trials; CPRS ADHD Index *T*-score ≤ 63; ADHD-RS Parent Total *T*-Score ≤ 63; ADHD-RS Teacher Total *T*-Score ≤ 63

Summary and Conclusions

The above review has revealed that long-acting formulations are effective in the management of ADHD and are a useful addition to the clinical repertoire. Although there is limited evidence, studies suggest that ER stimulants are equivalent to multiple doses of IR. While effect sizes are somewhat smaller for *Strattera* than ER stimulants, numbers-needed-to-treat are more similar and it is also to be considered an effective treatment of ADHD. Time course for the different formulations differ. Hazards differ for the two classes of drugs. Abuse potential appears to be low for all the drugs, with Strattera least likely and dexamfetamine most likely licensed drugs to be abused—but more research, especially in relation to adolescent diversion and misuse, is required. Treatment in adulthood is appropriate but great caution is required in relation to pre-school children. Costs vary and cost-effectiveness calculations are not yet adequate to guide practice.

More specifically it is recommended that

- Long-acting preparations should be available and used.
- They should not replace short-acting drugs (which will be the initial treatment for many children for reasons of cost and flexibility of dosing). Individual clinical choice is needed.
- Both ATX (*Strattera*) and extended-release preparations of stimulants should be available. The choice will depend upon the circumstances:
- *If treatment is starting with a long-acting preparation*, then start with extended-release methylphenidate and proceed to *Strattera* if the former is unhelpful. The choice of extended-release methylphenidate will depend upon the profile of action required over time, and upon the availability of drug. *Strattera* may nevertheless be preferred as first choice if substance abuse or comorbid tics are a problem, if there is a strong family preference for a non-stimulant, if a 24-h action is particularly strongly required or if there is comorbid anxiety.
- *If a child has responded well to an immediate-release stimulant*, there may still be reasons to shift to extended-release—for example, to avoid the stigma or inconvenience of repeated dosing. An extended-release preparation of methylphenidate will then be preferred.
- If a child has suffered adverse effects on immediate-release methylphenidate, then the next step will often be to proceed to Strattera.
- *If a child has failed to respond to immediate-release methylphenidate*, because of lack of efficacy rather than adverse effect, then the next option is to try dexamfetamine or Strattera depending on the relative balance of advantages.

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Appendix 1

Excerpts from: "SIGN 50: A guideline developers' handbook Section 6: Forming guideline recommendations" [55]

These excerpts are included to assist the reader understand the grading system used in this guideline. They are not intended as a substitute for the full SIGN guidance and anyone wishing to explore this area further should consult the full guidance [55]:

"Guideline recommendations are graded to differentiate between those based on strong evidence and those based on weak evidence. This judgment is made on the basis of an (objective) assessment of the design and quality of each study and a (perhaps more subjective) judgment on the consistency, clinical relevance and external validity of the whole body of evidence. The aim is to produce a recommendation that is evidence-based, but which is relevant to the way in which health care is delivered and is therefore *implementable*.

It is important to emphasise that the grading does not relate to the *importance* of the recommendation, but to the strength of the supporting evidence and, in particular, to the predictive power of the study designs from which that data was obtained. Thus, the grading assigned to a recommendation indicates to users the likelihood that, if that recommendation is implemented, the predicted outcome will be achieved." SIGN grading system

Levels of evidence

1++	High quality meta analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1−	Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies, High quality case–control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case–control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2−	Case–control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendation

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good practice points

☑	Recommended best practice based on the clinical experience of the guideline development group

On occasion, guideline development groups find that there is an important practical point that they wish to emphasise but for which there is not, nor is their likely to be, any research evidence. This will typically be where some aspect of treatment is regarded as such sound clinical practice that nobody is likely to question it. These are marked in the guideline as Good Practice Points, and are indicated . It must be emphasised that these are *not* an alternative to evidence-based recommendations, and should only be used where there is no alternative means of highlighting the issue.

Appendix 2

Potential conflicts of interest

	UCB		Lilly		Janssen/McNeil		Medice		Shire		Cephalon		Novartis	
	A or C	Other	A or C	Other	A or C	Other	A or C	Other	A or C	Other	A or C	Other	A or C	Other
Asherson				X	X	X								
Banaschewski	X		X	X		X	X	X	X					
Buitelaar	X	X	X	X	X	X		X	X					
Coghill	X	X	X	X	X	X			X		X			
Danckaerts	X		X	X	X	X					X		X	X
Döpfner	X	X	X	X		X	X	X	X		X			
Faraone			X	X	X	X			X	X		X	X	X
Rothenberger	X		X	X	X	X	X	X			X			
Santosh	X		X	X		X								
Sergeant			X	X	X	X	X		X					
Sonuga-Barke	X	X	X	X		X			X					
Steinhausen	X		X	X										
Taylor														
Zuddas	X		X	X	X	X			X		X			X

Note—A or C = served in an advisory or consultancy role either personally or for ones employer. This includes advisory boards
Other—Paid public speaking/conference attendance support/unrestricted research support/meeting or conference grants

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