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Attention deficit hyperactivity disorder (ADHD) in children and adolescents

Prescribing in children and adolescents CHAPTER 5 Attention deficit hyperactivity disorder (ADHD) in children and adolescents ■ ■A diagnosis of ADHD should be made only after a comprehensive assessment by a specialist with expertise in ADHD.1 Appropriate psychological, psychosocial and behavioural interventions should be put in place. Drug treatments should be only a part of the overall treatment plan. ■ ■The indication for drug treatment is the presence of impairment resulting from ADHD despite environmental modifications, parent training (if appropriate), advice on parenting strategies and liaison with school. ■ ■Methylphenidate is the first-line treatment when medication is indicated. It is a central nervous system (CNS) stimulant with a large evidence base from trials. Most common adverse effects include insomnia, appetite suppression, raised blood pressure, raised pulse rate and growth deceleration. These adverse effects can usually be managed by treatment breaks or dose reduction, depending on the side effect. Long-term use in children is associated with lower height and weight.2 In the UK and elsewhere, there are several modified-release preparations with different release profiles available, including generic options. ■ ■Dexamfetamine is an alternative CNS stimulant. Effects and adverse reactions are broadly similar to methylphenidate, but there is somewhat less evidence for efficacy and safety than exists for methylphenidate. Dexamfetamine is probably more likely to be diverted and misused. Both methylphenidate and dexamfetamine are Controlled Drugs in most countries. This makes prescribing and dispensing more complex. ■ ■Lisdexamfetamine is a pro-drug – dexamfetamine is complexed with the amino acid lysine and in this form is inactive. It is broken down in red blood cells so that dexamfetamine is gradually made available. It therefore has a similar practical role to extended-release preparations of methylphenidate and, like them, is unlikely to be abused for

recreational or dependency-driven purposes. Several RCTs have established it as superior to placebo in children3,4 and adolescents.5 Effect size from preliminary research appears to be at least as great as that of osmotic-controlled release oral delivery system (OROS)-methylphenidate4 and it seems to have a similar range of adverse effects.6,7 Network meta-analyses found lisdexamfetamine to be more effective than methylphenidate8,9 and long-term data suggest that it can be considered as an alternative to extended-release methylphenidate.10 Lisdexamfetamine is also effective in pre-school children11 although it is not licensed for this age group. ■ ■Atomoxetine is a non-stimulant alternative.12–15 It may be particularly useful for children who do not respond to stimulants, where stimulant diversion is a problem or when 'dopaminergic' adverse effects (such as tics, anxiety and stereotypies) become problematic on stimulants. Parents should be warned of the possibilities of suicidal thinking and emerging liver disease and advised of the possible features that they might notice. Atomexetine is less effective than stimulants.9,13,16,17

598 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 5 ■ ■A licensed modified--release preparation of guanfacine is approved in the UK and elsewhere for use in children with ADHD. Guanfacine is an α2 agonist medication and can be considered as an alternative non--stimulant medication to atomoxetine.18 It is broadly as effective as atomoxetine.19 Although not licensed for adults in most countries, children started on guanfacine should probably continue as adults. ■ ■Another non-stimulant medication with evidence of effectiveness in the treatment for ADHD is the α2 agonist clonidine.20 Extended-release clonidine is widely used for ADHD in the USA but not licensed in most countries. ■ ■There is some evidence supporting the efficacy of tricyclic antidepressants21,22 but these are not recommended in clinical practice. ■ ■Bupropion9,23,24 seems to be efficacious and well tolerated. Modafinil also appears to have useful activity in children but not in adults with ADHD.9,25,26 Evidence supporting the use of these drugs is somewhat limited compared with standard treatments.9 Viloxazine is also effective27 and approved in the USA. ■ ■The use of second-generation antipsychotics28,29 for ADHD is not recommended.28,29 These may reduce hyperactivity in autism spectrum disorders30 but should not be prescribed for this indication. ■ ■Emerging ADHD pharmacotherapies31 include the SNRIs venlafaxine and -duloxetine, agomelatine, dasotraline (a serotonin, noradrenaline and dopamine reuptake inhibitor) and tipepidine (potassium channel inhibitor). ■ ■Comorbid psychiatric illness is common in children with ADHD. Stimulants are often helpful overall but are unlikely to be appropriate for children who have a psychotic illness. Problems with substance misuse should be managed in their own right alongside ADHD treatment32 and treatments need to be chosen carefully. ■ ■Combinations of stimulants and atomoxetine have been used, but there are few trials and no clear evidence for improved efficacy.33 ■ ■Combinations of stimulants and guanfacine are approved in some countries. There is some evidence that the combination might have additive effects on symptoms control.34 ■ ■Once stimulant treatment has been established, it is appropriate for repeat prescriptions to be supplied through general practitioners1 with reviews at least once a year by a healthcare professional with training and expertise in managing ADHD. Box 5.1 summarises the NICE guidelines for treating children with ADHD and Table 5.10 summarises prescribing in ADHD.

Prescribing in children and adolescents CHAPTER 5 Box 5.1 Summary of UK NICE guidance for ADHD in children1 ■ ■Drug treatment should only be initiated by a specialist and only after comprehensive assessment of mental and physical health and social influences. In children under 5 years, medication should be initiated after a second specialist opinion from an ADHD service with

expertise in managing ADHD in younger children (ideally a tertiary service) ■ ■An ADHD-focused group parent-training programme should be offered for parents or carers of children aged less than 5 years with ADHD. Environmental modifications need to be implemented in all cases. If ADHD symptoms are still causing a persistent significant impairment in at least one domain despite environmental modifications, medication can be offered following a baseline assessment ■ ■Methylphenidate, lisdexamfetamine, dexamfetamine, atomoxetine and guanfacine are recommended within their licensed indications ■ ■Methylphenidate (either short or long acting) is the first choice of medication ■ ■Consider switching to lisdexamfetamine for children aged 5 years and over and young people who have had a 6-week trial of methylphenidate at an adequate dose and not derived enough benefit in terms of reduced ADHD symptoms and associated impairment ■ ■Consider dexamfetamine for children aged 5 years and over and young people whose ADHD symptoms are responding to lisdexamfetamine but who cannot tolerate the longer effect profile ■ ■Offer atomoxetine or guanfacine to children aged 5 years and over and young people if they cannot tolerate methylphenidate or lisdexamfetamine or their symptoms have not responded to separate 6-week trials of lisdexamfetamine and methylphenidate, having considered alternative preparations and adequate doses ■ ■Monitoring should include measurement of height and weight (with entry on growth charts) and recording of blood pressure and heart rate. An electrocardiogram is not needed before starting stimulants* atomoxetine or guanfacine unless the person has any of the following: ■ ■History of congenital heart disease or previous cardiac surgery ■ ■history of sudden death in a first-degree relative under 40 years suggesting a cardiac disease ■ ■shortness of breath on exertion compared with peers ■ ■fainting on exertion or in response to fright or noise ■ ■palpitations that are rapid, regular and start and stop suddenly ■ ■chest pain suggesting cardiac origin ■ ■signs of heart failure ■ ■a murmur heard on cardiac examination ■ ■blood pressure that is classified as hypertensive for adults ■ ■a coexisting condition that is being treated with a medicine that may pose an increased cardiac risk A cardiology opinion should be sought if any of the above apply *The cardiovascular toxicity of stimulants remains poorly quantified. Some analyses show no adverse effect35 while population studies suggest increased risk of hypertension and other adverse outcomes.36

CHAPTER 5 Table 5.10 Prescribing in attention deficit hyperactivity disorder (ADHD). Medication Onset and duration of action Dose Notes Recommended monitoring/general notes Methylphenidate immediate release Branded products (Ritalin, Medikinet, Tranquilyn) and various generic preparations available37–39 Onset: 20–60 minutes Duration: 2–4 hours Initially 5–10mg daily titrated up in weekly increments of 5–10mg, to a maximum of 2.1mg/ kg/day in divided doses. Licensed maximum dose 60mg daily (or after specialist review up to 90mg daily)1 Methylphenidate usually first-line treatment in ADHD. Generally well tolerated40 For methylphenidate, dexamfetamine and lisdexamfetamine Monitor: ■ ■Blood pressure41 ■ ■Pulse ■ ■Height ■ ■Weight Monitor for insomnia, mood and appetite change and the development of tics,42 although some evidence suggests tics are not associated with psychostimulants43 Discontinue if no benefits seen in 1 month Controlled Drugs Methylphenidate modified release* An afternoon dose of immediate-release methylphenidate may be necessary in some children to optimise treatment. Concerta XL37,38,44–46 Bioequivalent versions: Affenid XL, Xaggitin XL, Matoride XL, Xenidate XL, Delmosart modified release Onset: 0.5 –2 hours Duration: 12 hours Initially 18mg in the morning, titrated up to a licensed maximum dose of 54mg daily (or after specialist review up to 108mg daily; NB unlicensed) 18mg = 15mg methylphenidate immediate release Consists of an immediate--release component (22% of the dose) and a modified- release component (78% of the dose).

Equasym XL47,48 Onset: 20–60 minutes Duration: 8 hours Initially 10mg in the morning, titrated up to a licensed maximum dose of 60mg daily Consists of an immediate- release component (30% of the dose) and a modified-release component (70% of the dose). Capsules can be opened and sprinkled. Medikinet XL Bioequivalent versions: Metyrol XL and Meflynate Onset: 20–60 minutes Duration: up to 8 hours Dose as for Equasym XL Consists of an immediate- release component (50% of the dose) and a modified-release component (50% of the dose). Capsules can be opened and sprinkled.49

Table 5.10 (Continued) Onset and duration of action Dose Notes Medication Ritalin XL50 Onset: 60 minutes Duration: 8–12 hours Dexamfetamine immediate release40,51 Initially 2.5–10mg daily, titrated up in weekly increments of 2.5–5mg, to a maximum of 20mg daily in divided doses (occasionally up to 40mg daily is necessary) Onset: 20–60 minutes Duration: 3–6 hours Lisdexamfetamine (Elvanse)3–5 Onset: 20–60 minutes Duration: 13+ hours Initially 20 or 30mg in the morning, titrated up to a licensed maximum dose of 70mg daily Atomoxetine53,54 Approximately 4–6 weeks (atomoxetine is a noradrenaline reuptake inhibitor) When switching from a stimulant, continue stimulant for first 4 weeks of therapy. For children <70kg: Initially 0.5mg/kg/day for 7 days, then increase according to response. Recommended maintenance dose 1.2mg/kg/day (in single or divided doses) and up to 1.8mg/kg/day, to a maximum of 120mg daily if necessary1 For children >70kg: Initially 40mg daily for 7 days, then increase according to response. Recommended maintenance dose 80mg daily Prescribing in children and adolescents Recommended monitoring/general notes Dose as for Equasym XL Consists of an immediate-release component (50% of the dose) and a modified- release component (50% of the dose). Considered to be less well tolerated than methylphenidate.40 Pro-drug, gradually hydrolysed to dexamfetamine Capsules can be opened and sprinkled.52 Licensed in adults CHAPTER 5 Less effective than stimulants (see text).13,17 Monitor: ■ ■Blood pressure56 ■ ■Pulse May be useful where stimulant diversion is a problem.55 ■ ■Height ■ ■Weight Monitor for insomnia, mood and appetite change and the development of tics. Licensed in adults Monitor young people and adults with ADHD for sexual dysfunction (that is, erectile and ejaculatory dysfunction) as potential adverse effects of atomoxetine. Not a Controlled Drug (Continued)

602 The Maudsley® Prescribing Guidelines in Psychiatry Table 5.10 (Continued) Onset and duration of action Dose Notes Medication Guanfacine modified release9,57 Approximately 1– 5 weeks58 (guanfacine is a central alpha2Aadrenergic receptor agonist) For child 6–12 years (body weight 25kg and above): Initially 1mg once daily; adjusted in steps of 1mg every week if necessary and if tolerated; maintenance 0.05–0.12mg/kg once daily (max. per dose 4mg) For child 13–17 years (body weight 34–41.4kg): Initially 1mg once daily; adjusted in steps of 1mg every week if necessary and if tolerated; maintenance 0.05–0.12mg/kg once daily (max. per dose 4mg) For child 13–17 years (body weight 41.5–49.4kg): Initially 1mg once daily; adjusted in steps of 1mg every week if necessary and if tolerated; maintenance 0.05–0.12mg/kg once daily (max. per dose 5mg) CHAPTER 5 For child 13–17 years (body weight 49.5–58.4kg): Initially 1mg once daily; adjusted in steps of 1mg every week if necessary and if tolerated; maintenance 0.05–0.12mg/kg once daily (max. per dose 6mg) For child 13–17 years (body weight 58.5kg and above): Initially 1mg once daily; adjusted in steps of 1mg every week if necessary and if tolerated; maintenance 0.05–-0.12mg/kg once daily (max. per dose 7mg) *For details of other preparations available outside the UK, see Cortese et al., 2017.59 Recommended monitoring/general notes Efficacy and tolerability data should be interpreted with caution.9 Similar monitoring to other medication for ADHD.

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