# 10 - Chapter 5 Prescribing in children and adolescents

# 01 - Principles of prescribing practice in childho

# Principles of prescribing practice in childhood and adolescence

The Maudsley® Prescribing Guidelines in Psychiatry, Fifteenth Edition. David M. Taylor, Thomas R. E. Barnes and Allan H. Young. © 2025 David M. Taylor. Published 2025 by John Wiley & Sons Ltd. Chapter 5 Principles of prescribing practice in childhood and adolescence Diagnosis can be difficult in children and comorbidity is very common. Treatment should generally target key symptoms rather than specific conditions. While a working diagnosis is beneficial to frame expectations and help communication with patients and parents, it should be kept in mind that it could take some time for the illness to evolve.1 Differences in pharmacokinetics and pharmacodynamics compared with adults can explain the more pronounced or unforeseen adverse reactions to medication in the young, as well as the differences in dose–effect relationships compared with those in adults.2 ■ ■Start low, go slow and monitor Depending on the age, dose starts lower than in adults or may be calculated in mg/kg per day terms.1,2 Titration of dose should proceed slowly, aiming for the minimum dose that adequately controls symptoms and has minimum adverse reactions. Regular reviewing of efficacy and tolerability should guide if treatment is necessary and requires continuation. ■ ■Polypharmacy in the severely ill Monotherapy is ideal. However, childhood-onset illness can be severe and may require treatment with psychosocial approaches in combination with more than one medication.1 Co-prescribing of medication for different disorders or symptoms is common. This complicates the interpretation of efficacy of each medicine1 and requires care with drug interactions and dose adjustments. ■ ■Adequate treatment duration Children are generally relatively more ill than their adult counterparts and will often require longer periods of treatment before responding. An adequate trial of treatment for those who are admitted for in-patient care may well be 8 weeks or more for depression or schizophrenia. Prescribing in children and adolescents

562 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 5 ■ ■Change one drug at a time Ideally changes should be made to one drug at a time and, if possible, remove a drug when

adding a new one. ■ ■Monitor outcome in more than one setting For symptomatic treatments (such as stimulants for attention deficit hyperactivity or ADHD), bear in mind that the expression of problems may be different in different settings (e.g. home and school). For example, a dose titrated against parent reports may be too high for the daytime at school. ■ ■Educate the child and parents on the treatment For some, the need for medication will be life-long. The first experiences with medications are crucial to long-term outcomes and adherence. Education regarding the target symptoms of the medication, likely adverse reactions and medication adherence should be addressed. Provide information on the monitoring required and how to identify adverse reactions. Patients and their guardians should be encouraged to ask for changes to their treatment regimen where they consider them ineffective or poorly tolerated. ■ ■Review long-term treatment As children develop and grow through adolescence, dose changes may be required and adverse reactions may emerge or wane. ■ ■Transition from paediatric to adult services It is essential that continuity of care is not lost when moving from paediatric to adult services as this can be distressing and increase the risk of relapse. Planning and co-ordination should start at an early stage to achieve a smooth transition.3 ■ ■Technical aspects of paediatric prescribing Most psychotropic drugs used in adults are not licensed for use in children or -adolescents.4 The Medicines Act 1968 and European legislation make provision for doctors to use medicines in an off-label or out-of-licence capacity or to use unlicensed medicines. Where possible a licensed preparation should be prescribed (Table 5.1), however it is recognised that the informed use of unlicensed medicines, or of licensed medicines in an 'off-label' way, is often necessary in paediatric practice. Individual prescribers are always responsible for ensuring that there is adequate information to support the quality, efficacy, safety and intended use of a drug before prescribing it.5 When writing a prescription in most countries, inclusion of age is a legal requirement in the case of prescription-only medicines for children under 12 years of age, but it is preferable to state the age for all prescriptions for children.

Prescribing in children and adolescents CHAPTER 5 Table 5.1 Psychotropic medications approved by the UK Medicines and Healthcare products Regulatory Agency (MHRA), European Medicines Agency and the US Food and Drug Administration for children and adolescents (January 2024).6–9 Condition UK MHRA approval only; age (years) European Medicine Agency;* age (years) US Food and Drug Administration; age (years) ADHD Amfetamine–dexamfetamine mixed salts – – 3+ -Amfetamine–dexamfetamine mixed salts extended release – – 6+ Atomoxetine 6+ 6+ 6+ Clonidine extended release – – 6–17 Dexamfetamine 6–17 6–17 3–16 Dexamfetamine sustained release – – -6–16 Dexmethylphenidate – – 6+ Guanfacine extended release 6–17 6–17 6–17 Lisdexamfetamine 6+ 6+ 6–17 Methamfetamine – – 6–17 Methylphenidate 6+ 6–18 6+ Viloxazine – – 6+ Anxiety disorders Duloxetine – – GAD 7+ Escitalopram – – GAD 7+ Autism spectrum disorder (irritability) Aripiprazole – – 6–17 Risperidone – – 5–17 Bipolar disorder (depressive episodes) Lurasidone – – 10+ Olanzapine–fluoxetine combination – – 10+ Bipolar disorder (manic or mixed episodes) Aripiprazole Manic episodes 13+ Manic episodes 13+ Manic or mixed episodes 10+ Asenapine – – 10+ Lithium – – 7+ Lithium extended release – – 12+ Olanzapine – – 13+ Quetiapine extended release – – 10+ (Continued )

564 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 5 Condition UK MHRA approval only; age (years) European Medicine Agency;* age (years) US Food and Drug Administration; age (years) Risperidone – – 10+ Ziprasidone – 10+ – Conduct disorder Risperidone 5–18 5–18 – Depressive disorder Amitriptyline – – 12+ Escitalopram – – 12+ Fluoxetine 8+ 8+ 8+ Enuresis

Amitriptyline 6–17 6–17 – Imipramine 6–17 5–18 6–17 Insomnia (in autism spectrum disorder or Smith Magenis syndrome) Melatonin extended release 6–17 2–18 – Insomnia (in ADHD) Melatonin immediate release 6–17 – – Insomnia (short term) Promethazine 5+ – – Obsessive compulsive disorder Clomipramine – – 10+ Fluoxetine – – 7+ Fluvoxamine 8+ 8+ 8+ Sertraline 6+ 6+ 6+ Schizophrenia Aripiprazole 15+ 15+ 13+ Brexpiprazole – – 13+ Lurasidone 13+ – 13+ Olanzapine – – 13+ Paliperidone 15+ 15+ 12+ Quetiapine – – 13+ Risperidone – – 13+ Sulpiride 14+ 6+ – Tourette’s disorder Aripiprazole – – 6–18 *Approvals may differ in individual countries. GAD, generalised anxiety disorder. Table 5.1 (Continued)

# 02 - References

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# 03 - Depression in children and adolescents

# Depression in children and adolescents

# 04 - Diagnostic issues

# Diagnostic issues

# 05 - Clinical guidance

# Clinical guidance

566 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 5 Depression in children and adolescents Diagnostic issues Approximately 15% of young people experience depression by age 18 years and these young people often have significant functional impairment and risk of harm.1 Compared with depressed adults, young people with depression tend to experience more irritability, loss of energy, insomnia and weight change, and less anhedonia and concentration problems.2 These symptoms can overlap with and appear similar to other disorders or can be minimised and incorrectly attributed to typical teenage development, making diagnosis challenging. Assessments should therefore be undertaken by clinicians who understand developmental variations and can accurately identify depression in young people.3 Clinical guidance For mild depression in children and adolescents, the UK National Institute for Health and Care Excellence (NICE) guidelines4 and American Academy of Child and Adolescent Psychiatry (AACAP) practice parameter3 recommend that supportive care or psychological intervention should be considered as first-line treatment, and that antidepressant medication should not be prescribed. For moderate to severe depression in young people, these same guidelines recommend offering psychological therapy, either alone or in combination with antidepressant medication. In addition, the AACAP practice parameter recommends that antidepressant medication alone could be considered, particularly if the presentation is severe and the patient is unable to engage in talking therapy, if psychological interventions are not available or if this is the patient’s and family’s preference. These guidelines were informed by research evidence for the effectiveness of selective serotonin reuptake inhibitors (SSRIs) in treating depression in young people. For example, a seminal large UK National Institute of Mental Health (NIMH) funded randomised controlled trial (RCT) – the Treatment of Adolescents With Depression Study (TADS)5 – found a fluoxetine response rate of 61% over the acute (12-week) phase, which was significantly higher than the placebo response rate of 35%, giving a number needed to treat (NNT) of 4.5 Subsequent systematic reviews and meta-analyses, which include this trial and others, have provided further evidence demonstrating that SSRIs are effective at improving symptoms and functioning, and are largely acceptable treatments for depression in young people. However, several individual studies and systematic reviews studies report less certain effects6–10 and a 2021 Cochrane review described antidepressant effects as ‘small and unimportant’.11 The current evidence base is unclear about whether SSRI medications alone, psychological therapy alone or combined treatment is most effective for treating depression in children and adolescents. TADS found that fluoxetine alone or in combination with cognitive behavioural therapy (CBT) might accelerate treatment response, and that adding CBT might decrease adverse effects including suicidality, so enhancing the safety of fluoxetine.5,12 However, other studies have not replicated this finding,13,14 including the Adolescent Depression Antidepressants and Psychotherapy Trial (ADAPT), which found no benefit in combining fluoxetine with CBT over fluoxetine alone.15 A network

# 06 - Prescribing for depression in children and ad

# Prescribing for depression in children and adolescents

Prescribing in children and adolescents CHAPTER 5 meta-analysis comparing several treatments for depression in children and adolescents also found that combined fluoxetine and CBT was no more effective than fluoxetine alone but found that this combination was more effective than CBT alone.16 Prescribing for depression in children and adolescents Before prescribing ■ ■Undertake a comprehensive assessment: Establish a clinical diagnosis of depression. Exclude differential diagnoses, including psychiatric disorders (such as bipolar affective disorder), medical disorders (such as endocrine disorders) and medication-related effects (such as steroid adverse effects). Identify any comorbid psychiatric or medical conditions. Consider contraindications to SSRIs and potential interactions. Assess risk of harm to self and others. Formulate considering factors that could predispose, precipitate and perpetuate depression, such as family history of psychiatric disorders (including depression and bipolar affective disorder) and environmental stressors (including victimisation and other adverse experiences). If any co-occurring problems are identified, these should be addressed and prioritised based on a comprehensive formulation. ■ ■Measure baseline severity: Measures of depression symptoms include the clinician- administered Children’s Depression Rating Scale-Revised (CDRS-R)17,18 and the childand parent-reported Mood and Feelings Questionnaire (MFQ)19 or Revised Children’s Anxiety and Depression Scale (RCADS).20 Measures of functional impairment include the Children’s Global Assessment Scale (CGAS).21 ■ ■Obtain informed consent: Discuss the nature, course and treatment of depression, potential adverse effects of medication, delay in onset of treatment effects, plan for monitoring and maintenance of medication and potential discontinuation effects. ■ ■Develop a safety plan: In all but exceptional circumstances, a parent or carer should be responsible for the secure storage of medication for a child or adolescent. Advise the young person and their parent/carer of professionals or services they should contact if they experience significant adverse effects, risk of harm or worsening symptoms. What to prescribe ■ ■Fluoxetine is the recommended first-line medication for depression in children and adolescents.3,4 It has the strongest current evidence for

efficacy,6,9,11,16,22,23 showing moderate effects in reducing depression symptoms versus placebo (standardised mean difference = 0.51).16 In the UK, NICE states that fluoxetine is the only antidepressant for which clinical trial evidence shows that benefits outweigh risks.4 Fluoxetine should be started at a dose of 10mg daily which can be increased after 1 week to the minimum therapeutic dose of 20mg daily. Higher doses (up to 40–60mg daily) may be considered, particularly in older children of higher body weight or when, in severe illness, an early clinical response is considered a priority.4,5,15,24 The long half-life of fluoxetine may be beneficial for adolescents because it confers a reduced risk of discontinuation effects or relapse if doses are delayed or missed.25 Fluoxetine is approved for treatment of depression in patients aged 8 years and over by the US Food and

 (FDA), and by the European Medicines Agency and the UK Medicines and Healthcare products Regulatory Agency (MHRA) if the young person has moderate to severe depression and has not responded to psychological therapy.26 ■ ■Sertraline and escitalopram have also been found to be more effective than placebo for treating depression in young people6,22 and should be considered as alternatives if fluoxetine is not tolerated. Sertraline and escitalopram should also be started at low doses (25–50mg daily and 5–10mg daily, respectively) and titrated to therapeutic doses (50–-200mg daily and 10–20mg daily, respectively). The half-lives of sertraline, escitalopram and some other antidepressants may be shorter in young people than adults, so twice daily dosing could be considered to prevent discontinuation symptoms.27 Escitalopram is approved by the FDA for treatment of depression in patients aged 12 years and over. ■ ■Duloxetine and venlafaxine may be effective but are relatively poorly tolerated.28 ■ ■Agomelatine was more effective than placebo in children aged 7–11 years and showed similar efficacy to fluoxetine. A dose of 10mg seems to be effective. Agomelatine is extremely well tolerated but not licensed for children or adolescents. Liver function test (LFT) changes occurred in 1% of participants.29 Vortioxetine was no more effective than placebo in a large study of 12–17-year-old children.30 ■ ■For children and adolescents who have significant depressive symptoms resulting in distress or impairment despite an adequate trial of an SSRI alone, consider combination SSRI and psychological therapy. There is some limited evidence that combination treatment may be more beneficial than SSRI alone for some young people.6,31–33 ■ ■For children and adolescents who have significant depressive symptoms resulting in distress or impairment despite adequate trials of an SSRI (fluoxetine) and psychological therapy, consider a switch to a different SSRI (sertraline, escitalopram).4,31 This guidance is largely based on the Treatment of Resistant Depression in Adolescents (TORDIA) trial,24 the only RCT that has examined the comparative efficacy of different treatment strategies for SSRI-resistant depression in young people.24 This trial found that many participants improved when switched to another SSRI or venlafaxine (response rate 47% and 48%, respectively) and improved even more when this medication switch was combined with starting concurrent CBT (response rate 55% vs 41% without CBT) after 12 weeks of treatment. A switch to an SSRI was just as efficacious as a switch to venlafaxine but had less frequent and severe side effects, so an SSRI switch is preferred. ■ ■If limited response despite adequate trials of these medications and psychological therapy, consider augmenting SSRI treatment with another medication such as a second-generation antipsychotic or lithium. (Also consider augmentation if there has been partial response to an SSRI.31) Alternatively, consider switching to an antidepressant from a different class, for example mirtazapine34 – especially if poor sleep is a problem. There are no RCTs testing the effectiveness of these strategies in children or adolescents, and so this guidance is largely

based on evidence from studies of adults with treatment-resistant depression, in addition to very limited follow-up of TORDIA participants receiving open-label treatment.31,35 ■ ■Finally, if still no response to these medications and the young person’s depression is very severe, ketamine, repetitive transcranial magnetic stimulation (rTMS) or electroconvulsive therapy can be considered. These interventions have an evidence base and

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# After prescribing

Prescribing in children and adolescents CHAPTER 5 are approved for use in adults with treatment--resistant depression, but there is no substantial evidence in children and adolescents.31 With regard to ketamine, or its enantiomer esketamine, emerging evidence suggests that it may be effective and adequately tolerated in adolescents with treatment-resistant depression based on a small number of studies, including two small RCTs.36–38 Considering rTMS, initial evidence suggested that it may be effective, again based on a small number of studies and a small RCT, but a larger RCT found no evidence of effectiveness.39 Electroconvulsive therapy (ECT) has limited evidence of effectiveness in young people, although one randomised trial in adolescents showed good effect against both depression and suicide.40 Therefore, these treatments' unknown potential effects on the developing brain need to be considered carefully and weighed up against the risks of not attempting these treatments.41 Further research is greatly needed to inform clinical decisions.42 ■ ■NICE warns against prescribing paroxetine, venlafaxine, tricyclic antidepressants or St John's wort for depression in young people, because of potential adverse effects and interactions.4 Table 5.2 summarises medication treatment for depression in children and adolescents. After prescribing Acute phase ■ ■Monitor for adverse effects regularly, for example weekly for the first 4  weeks. Children and adolescents generally tolerate SSRIs well. Potential adverse effects include those experienced by adults, described in Chapter 3. Additionally, young people taking SSRIs have a small increased risk of suicidality and switch to mania, as well as activation effects (see 'Specific issues' later in this chapter). Therefore, risk of harm, mood and behaviour should be monitored closely and addressed.3,4,6,31 ■ ■After 4  weeks of SSRI treatment at a therapeutic dose, assess response including depression severity using the measures completed at baseline. Most therapeutic effects appear by 4 weeks.43 ■ ■If partial or non--response, consider the possibility of poor treatment adherence, inaccurate diagnosis, comorbidity or modifiable maintaining factors. Table 5.2 Summary of pharmacotherapy for depression in children and adolescents.3,4,6,31 Medication Starting dose Therapeutic dose range First line Fluoxetine 10mg/day 20–60mg/day Second line Sertraline Escitalopram Citalopram* 25–50mg/day -5–10mg/day 10mg/day 50–200mg/day 10–20mg/day 20–40mg/day Subsequently Consider augmentation of antidepressant with second-generation antipsychotic or lithium.† Consider switching to an antidepressant from a different class, such as mirtazapine. *Caution advised in cardiac or hepatic disease. †No randomised controlled trials available in young people (but there is evidence from adult trials).

# 08 - Specific issues

# Specific issues

570 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 5 ■ ■If none of these factors explains the continued depressive symptoms and the young person does not have adverse effects, consider increasing the dose. Reassess every 4 weeks.3,31 This recommendation is largely based on evidence from adult depression trials, which have demonstrated small but significant improvements in depression symptoms with higher doses of SSRIs,44 as there has been only limited research on this topic in children and adolescents.45 ■ ■If adverse effects develop, consider reducing the dose to the highest tolerated dose. ■ ■If partial or non-response after 8 weeks of the maximum recommended (or highest tolerated) therapeutic dose of an SSRI, consider the medication changes outlined earlier.31 Maintenance phase Continue medication for -6–12 months after remission to reduce the risk of relapse. Consider a longer maintenance phase if depressive episodes were recurrent or chronic.3,4,6,31 Again, this recommendation is largely based on evidence from adult depression trials, in addition to very limited research in children and adolescents.46,47 Discontinuation phase Discontinuation may be considered after the maintenance phase. This is best undertaken during a period of low stress. Taper medications slowly and hyperbolically (see Chapter 3) to minimise the risk of discontinuation symptoms.3,4,6,31 Specific issues ■ ■Age The evidence base for these recommendations is stronger for adolescents than for children, so caution should be higher when considering prescribing for children. There has been no research investigating antidepressant medication use in pre-school children, and medications are not recommended for this age group.4,22 ■ ■Suicidality Antidepressant medication has been linked to an increased risk of suicidality in young people, which led to warnings issued by the US FDA, the European Medicines Agency and the UK MHRA in 2003–2005. Subsequent meta-analyses have also found evidence of this association with reported suicidality,11,22,48 particularly for venlafaxine,16,23 as well as a link with aggression.49 A meta--analysis of reported suicidal thoughts or attempts in depression trials found a pooled absolute rate in antidepressant-treated young people of 3% and in those receiving placebo of 2%, giving a number needed to harm (NNH) of 112 (note these rates are low, probably because those with high risk of suicidality were often excluded from trials).50 Concern has also been expressed about emergent suicidality with escitalopram.51 To date, there has been no link between antidepressant use and completed suicides, but extreme care should be exercised. Untreated depression is a significant risk factor for suicidality. After the FDA warning on antidepressant use in children and adolescents, antidepressant use declined, untreated depression increased and suicide rates increased.52,53 Given the risks of untreated depression, including completed suicide and impaired functioning, and that many more patients benefit from SSRIs than those who experience these serious adverse events, it is thought that the benefits of antidepressants, particularly fluoxetine, are

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Prescribing in children and adolescents CHAPTER 5 likely to outweigh these risks in moderate to severe depression. Nonetheless, it bears repeating that the risk of suicide should be very carefully monitored.3,4,6,31 ■ ■Activation and manic switch Activation adverse effects of antidepressant - medication – including increased activity, restlessness and agitation – occur more commonly in children than in adolescents or adults. These effects, including mild symptoms, may occur in about 10% of children with depression taking SSRIs.54,55 They are usually a transient response to starting medication or increasing dose and should be differentiated from manic switch. Conversion to mania is rarer but is observed more often in young people taking antidepressants than in adults.56,57 However, there is no clear evidence that this switch is caused by antidepressants. References


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# 10 - Bipolar disorder in children and adolescents

Bipolar disorder in children and adolescents

# 11 - Clinical guidance

# Clinical guidance

Prescribing in children and adolescents CHAPTER 5 Bipolar disorder in children and adolescents Clinical guidance Before prescribing ■ ■Establish clinical diagnosis informed by structured instrument assessment if possible. Symptom checklists should be avoided, especially in primary care. Try to monitor symptom patterns prospectively with mood or sleep diaries. If in doubt, seek specialist advice early on. ■ ■Explain the diagnosis to the patient and family and invest time and effort in psycho education. This is likely to improve adherence and help children and adolescents and their families appreciate early warning signs of a relapse. Furthermore, there is evidence that such approaches reduce relapse rates, at least in adults.1 ■ ■Measure baseline symptoms of mania (e.g. Young Mania Rating Scale2 [YMRS] and the parent YMRS3), depression (e.g. Children's Depression Rating Scale4 [CDRS]) and impairment (e.g. Clinical Global Impression – BD version5). Use these to set clear and realistic treatment goals. ■ ■Measure baseline height, weight, waist and hip circumference, pulse, blood pressure and electrocardiogram (ECG) and obtain baseline bloods as appropriate (fasting blood glucose, HbA1c, fasting lipid profile, full blood count [FBC], urea and electrolytes [U&E], creatine kinase, LFTs, prolactin and thyroid function). What to prescribe ■ ■Tables 5.3, 5.4, 5.5 and 5.6 summarise medication use in bipolar mania and depression and acute mania. ■ ■For the treatment of mania and hypomania in children and adolescents, UK NICE guidelines suggest following the same recommendations as for adults – second- generation antipsychotics (SGAs) may be used as first-line treatment, and mood stabilisers (MS) can be added after a failure of two trials of SGAs.6 The difference in comparison with adult guidelines is that NICE recommends that SGAs should not be routinely offered for more than 12 weeks. This information should be shared with the child or adolescent and their family. ■ ■SGAs seem to show greater short-term efficacy (effect size [ES] = 0.65 compared with placebo) than MS (ES = 0.20 compared with placebo) in youth, according to a 2010 meta-analysis.7 ■ ■SGAs produce significantly greater weight gain (particularly olanzapine) and somnolence in children and adolescents compared with adults,7 although weight gain assessment is made complicated by normal growth at this time of life. ■ ■Valproate should be completely avoided in all adolescents. ■ ■Adherence to lithium cannot be assumed and blood level testing may be difficult in adolescents. ■ ■Overall, we recommend the use of SGAs as first line for the acute treatment of mania in children and adolescents (Tables 5.3 and 5.5). ■ ■It is helpful to document family history of response and non-response to pharmacological treatment as there is evidence to suggest that pharmacological response, at least for lithium, runs in families.8

# 12 - Other treatments

# Other treatments

574 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 5 After prescribing ■ ■Assess and measure symptoms on a regular basis to establish effectiveness. ■ ■Monitor weight, height and waist to hip circumference at each visit and repeat all fasting bloods at 3 months (then every 6 months). Offer advice on healthy lifestyle and exercise. ■ ■The duration of most medication trials is 3–5 weeks – this is the period over which most improvement is anticipated to occur. This should guide decisions about how long to try a single drug in a patient. A complete absence of response at 2 weeks should prompt consideration of a switch to another SGA (or a dose increase where labelling allows). ■ ■If there is no response, check adherence, measure blood levels where possible and consider increasing the dose. Consider concurrent use of an SGA and MS. ■ ■Judicious extrapolation of the evidence from adults9 is required because of the very limited evidence base in youths with bipolar disorder. This includes treatment duration and prophylaxis.6,7,10 Maintenance treatment should follow adult guidelines. Consider the use of lithium early in the course of treatment, either by switching to lithium monotherapy prophylaxis or as an adjunct to a successful acute medication. Lithium has therapeutic advantages over other options in adults but should only be used where adherence is assured. Specific issues ■ ■Bipolar depression is a common clinical challenge and its treatment has been studied much less in youths than in adults (Tables 5.4 and 5.6). Antidepressants should be used rarely and with care for the minimum duration possible and only in the presence of an antimanic agent.6 There is limited evidence for the benefit of antidepressants in bipolar depression in adults.11 Because of the dearth of trials in youth, we are compelled to extrapolate from adult studies,6 which suggest use of the -olanzapine/fluoxetine combination as the most effective treatment, along with lurasidone, which is supported by evidence from several trials in children aged 10–17 years.12–14 The metabolic effects of olanzapine arguably make it a second-line choice after lurasidone. ■ ■The exact relationship between ADHD and bipolar depression is still debated. Some evidence suggests that stimulants in children with ADHD and manic symptoms may be well tolerated15 and that they may be safe and effective to use after mood stabilisation.15 Caution and experience with prescribing these drugs are required. ■ ■The DSM-5 category of disruptive mood dysregulation disorder (DMDD) includes severely irritable children (who were commonly misdiagnosed as having bipolar depression in the USA). There is no established treatment for DMDD. Lithium is ineffective16 but SSRIs and psychological treatment options, such as parenting interventions, may be considered.17 Other treatments ■ ■Adjunct treatments including psychoeducation, CBT and especially family--focused interventions can enhance treatment and reduce depression relapse rates in bipolar disorder.18

Prescribing in children and adolescents CHAPTER 5 ■ ■There is emerging evidence that a combination of omega-3 fatty acids with inositol is effective in mania and hypomania in children

aged 5–12 years.19 Confirmatory trials are needed. ■ ■Cariprazine may be effective in young people but evidence is limited.20 ■ ■The use of high-frequency rTMS in adolescents with treatment-resistant unipolar depression is only supported by open-label studies21 and no RCT has been done in youth with either unipolar or bipolar depression. Therefore, its use is still considered experimental. One randomised sham-controlled study found rTMS ineffective in treating acute mania in youth (as an add-on to standard pharmacotherapy).22 ■ ■One small trial supported the adjunctive use of melatonin (6mg/day) in adults with mania.23 Evidence is not yet sufficient to recommend its use in children. Table 5.3 Pharmacological treatments of mania in children and adolescents. Medication Comment Lithium Lithium is cleared relatively quickly in children so twice daily dosing will be required, especially when using liquid or non-modified-release preparations.24 One double-blind placebo-controlled randomised trial25 showed significant reductions in substance use and clinical ratings after 6 weeks in adolescents with bipolar disorder and comorbid substance misuse. In a double-blind placebo- controlled discontinuation trial (N = 40) over 2 weeks, no significant difference in relapse rates were found between lithium and placebo.26 A later double-blind placebo-controlled study (N = 81), over 8 weeks, demonstrated a significantly larger change in YMRS score in lithium-treated youths. There was a significant increase in thyrotropin with lithium, but no difference in weight gain.27 Lithium and divalproex did not differ in an 18-month maintenance trial in youths (N = 60) who initially stabilised on combination pharmacotherapy of lithium and divalproex.28 However, given the compelling evidence for lithium maintenance and prophylaxis in adults, we recommend that clinicians consider its use in adolescents in preference to valproate. Valproate should be avoided in adolescents in any case. A meta-analysis29 found lithium to be ‘clearly inferior’ to risperidone in mania. Lithium may also be inferior to quetiapine in the treatment of mania in children and adolescents.30 One small 6-month study found higher relapse rates in those who discontinued lithium compared with those who continued.31 Another naturalistic 8-month study showed lithium to be effective and well tolerated.32 Valproate In an RCT (N = 150)33 divalproex ER (titrated to clinical response or 80–-125mg/L) did not lead to significant differences in mean YMRS compared with placebo at 4 weeks. (Also see risperidone and quetiapine sections below.) Valproate should be avoided in all peri- and post-pubertal children and adolescents. Oxcarbazepine A double-blind placebo-controlled study (N = 116) did not show significant differences between placebo and oxcarbazepine (mean dose 1515mg/day) in reducing mania rating at 7 weeks.34 (Continued )

 Medication Comment Olanzapine A double-blind placebo-controlled study (N = 161)35 showed olanzapine (5–20mg/day) to be significantly more effective than placebo over a period of 3 weeks. There was greater weight gain in the treatment group (weight gain was 3.7kg for olanzapine vs 0.3kg for placebo) and associated significantly increased fasting glucose, total cholesterol, AST, ALT and uric acid. The addition of topiramate reduces weight gain by more than a half.36 Risperidone A double-blind placebo-controlled study (N = 169) showed risperidone (at doses 0.5–2.5 or 3–6mg) to be more effective than placebo in YMRS mean score reduction in a 3-week follow-up.37 The lower dose led to the same benefits at a lower risk of adverse effects. Sleepiness and fatigue were common. Mean weight increase in treatment groups was 0.7kg vs 1.7kg for the low-dose arm and 1.4kg for the high-dose arm. In the Treatment of Early Age Mania (TEAM) study, higher response rates (and metabolic side effects) occurred with risperidone (mean dose 2.57mg) than with lithium (mean level 1.09mmol/L) and divalproex sodium (mean level 113.6mg/L).38 A randomised follow-up of this study showed again the superiority of risperidone as an alternative treatment for non--

responders to lithium and divalproex sodium, and as an add-on treatment to partial responders to the two drugs.39 These results need to be interpreted with caution as the definition of mania was broader than that used in some countries. The same caveat applies when considering another double-blind placebo-controlled trial showing significantly better results for risperidone (mean dose 0.5mg) than for valproic acid (mean level 81mg/L) in 3–7-year-old children supposedly diagnosed with mania.40 Quetiapine A double-blind placebo-controlled study (N = 277)41 showed quetiapine (at doses of 400 or 600mg/day) to be significantly better than placebo in reducing mean YMRS scores at 3 weeks. The most common side effects included somnolence and sedation. Weight gain was 1.7kg in the quetiapine group and 0.4kg for placebo. Quetiapine is effective as an adjunct to valproate compared with valproate alone (N = 30, 6 weeks)42 and was as effective as valproate in a double-blind trial (N = 50, 4 weeks).43 Aripiprazole A double-blind placebo-controlled study44,45 showed aripiprazole (at doses 10 or 30mg/day) to be significantly better than placebo at both 4 weeks (N = 296)44 and 30 weeks (N = 210).45 There was a higher incidence of extrapyramidal side effects in the treatment groups (especially the higher dose). Weight gain was significantly more common in the treatment groups compared with placebo (3.0kg for placebo; 6.5kg for the low-dose arm and 6.6kg for the high-dose arm) at week 30. Ziprasidone A double-blind placebo--controlled trial (N = 237)46 showed ziprasidone (at flexible doses 40–160mg) to be more effective than placebo in reducing mean YMRS scores at 4 weeks. Sedation and somnolence were the most common side effects, while it demonstrated a neutral metabolic profile and no QTc prolongation. A second RCT of 171 participants showed broadly similar outcomes.47 Asenapine A 3-week double--blind placebo-controlled study (N = 350) demonstrated statistical superiority of asenapine over placebo for each of the doses used (2.5, 5 or 10mg BD), with significant difference as early as day 4. However, many side effects were reported, including weight gain of more than 7% of baseline in 8–12% of the asenapine group vs 1.1% in the placebo group, metabolic changes (increase in insulin, lipids, glucose), as well as somnolence, sedation, oral hypoaesthesia and paraesthesia.48 ALT, alanine transaminase; AST, aspartate aminotransferase; ER, extended release; MS, mood stabilisers; YMRS, Young Mania Rating Scale. Table 5.3 (Continued)

Prescribing in children and adolescents CHAPTER 5 Table 5.4 Pharmacological treatments of bipolar depression in children and adolescents. Medication Comment Olanzapine/ fluoxetine combination A large study (N = 255) of the olanzapine/fluoxetine combination (either 6/25 or 12/50mg daily) for 8 weeks49 showed an advantage for the combination. Most frequent side effects were weight gain (4.4kg for olanzapine/fluoxetine and 0.5kg for placebo), somnolence and hyperlipidaemia. The olanzapine/fluoxetine combination is recommended by UK NICE guidelines,6 along with quetiapine, as first-line treatment for bipolar depression in children and adolescents, as in adults. Although the olanzapine/fluoxetine combination is not currently available as a single preparation in the UK or European Union, its effects can be achieved by combining olanzapine and fluoxetine (e.g. 5/20 or 10/40mg). Lurasidone Lurasidone has been shown to be effective in bipolar depression in adults-50–52 and it does not seem to cause weight gain and other metabolic disturbances. It is also safe and effective in treating schizophrenia in adolescents.53 Lurasidone was effective in bipolar depression in children (10–17 years) both acutely12 and in a 2-year follow-up study.14 Dose ranged from 18.5mg (20mg) to 74mg (80mg). Lurasidone may be the preferred antipsychotic in children on account of its good tolerability.54 In fact, a 2022 network meta-analysis14 considered lurasidone to be the optimal treatment for bipolar depression in youths. Quetiapine A small study in 32 adolescents,55 followed by a larger RCT (N = 193),56 failed to show effectiveness. The second study had a very high placebo response, which is not usually seen in adult quetiapine studies57

and which may reflect issues in diagnosing mood disorders in multisite studies.58 A 2022 meta-analysis suggested quetiapine was ineffective in bipolar depression in young people.14 Lamotrigine Lamotrigine has only modest, if any, effects in adult bipolar depression59 and it has not been studied in RCTs for the treatment of acute bipolar depression in children and adolescents and is, therefore, not recommended as a first-line drug. Moreover, a placebo-controlled randomised withdrawal study of adjunctive lamotrigine for bipolar disorder in youth, lasting over 36 weeks, failed to show any benefit in preventing time to occurrence of a bipolar event.60 Table 5.6 Recommended first-line treatments for bipolar depression.* Lurasidone 18.5mg (20mg) to 74mg (80mg) daily Olanzapine/fluoxetine 6/25mg to 12/50mg daily *Continue acutely effective dosing regimen as prophylaxis and consider need for lithium if not already prescribed. Table 5.5 Recommended first-line treatments for acute mania.* Aripiprazole 10mg daily Risperidone 0.5–-2.5mg daily Olanzapine 5–20mg daily Quetiapine Up to 400mg daily Asenapine 2.5–10mg twice daily *Continue acutely effective dosing regimen as prophylaxis and consider need for lithium if not already prescribed.

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# 14 - Psychosis in children and adolescents

# Psychosis in children and adolescents

580 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 5 Psychosis in children and adolescents Schizophrenia is rare in children, but the incidence increases rapidly in adolescence. A detailed developmental and physical assessment is always needed before the diagnosis is made.1,2 Early-onset schizophrenia spectrum (EOSS) disorder is often chronic and in the majority of cases requires long-term treatment with antipsychotic medication.3 However, there is very limited RCT evidence for maintenance treatment with antipsychotics beyond 8 weeks,4 although there are supportive open-label studies.5 There have been several RCTs of first--generation antipsychotics, many of them using very high doses and all of them showing high rates of extrapyramidal side effects (EPSEs) and significant sedation.5 Treatment-emergent dyskinesias can also be problematic6 even when smaller doses are used.7 First-generation antipsychotics should be avoided in children and adolescents. There have also been a number of RCTs of SGAs in EOSS disorder. Olanzapine,8–10 risperidone,8,9,11,12 aripiprazole,13,14 quetiapine,14,15 paliperidone16 and lurasidone17 have all been shown to be effective in the treatment of psychosis in younger people. There is meta-analytical evidence suggesting broadly comparable efficacy of individual SGAs, with the exception of ziprasidone and asenapine which are relatively less effective.18,19 Importantly, neither aripiprazole nor lurasidone seems to have an effect on QT in - adolescents.20,21 At the time of writing there is no RCT evidence supporting any additional benefit for long-acting antipsychotic injections in younger people, although advantages observed in adults might be assumed to be relevant in younger people. Indeed, a 2023 review of 119 reported adolescent cases suggested good outcomes.22 Children and adolescents are at greater risk than adults for adverse effects such as extrapyramidal symptoms, raised prolactin, sedation (even with aripiprazole14), weight gain and metabolic effects.23 Metformin has RCT evidence for the reduction of antipsychotic-related overweight/obesity in children and adolescents with EOSS - disorder, while healthy lifestyle education alone does not.24 There is evidence that clozapine is effective in treatment-resistant psychosis in adolescents, although this population may be somewhat more prone to neutropenia and seizures than adults.25–29 Based on data obtained from the treatment of younger adults, olanzapine should probably be tried before moving to clozapine30 because there is a palpable chance that it will be effective, although clozapine is clearly more effective than olanzapine in adolescents.26,27 Overall, algorithms for treating psychosis in children

and adolescents are the same as those for adult patients. In the UK, NICE31 recommends oral antipsychotics in conjunction with family interventions, individual CBT and art therapy. Starting doses should be at the lower end of, or below, the adult range. Antipsychotics should not be offered with the aim of decreasing the risk of developing psychosis;31–33 they are indicated only in the treatment of psychosis. When prescribing antipsychotics in children and adolescents always measure baseline parameters and monitor as outlined in the guidance in the chapter on schizophrenia (see Chapter 1). For children and adolescents also include waist and hip circumference, assessment of any movement disorders and assessment of nutritional status, diet and level of physical activity.31

# 15 - References

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# 16 - Anxiety disorders in children and adolescents

## Anxiety disorders in children and adolescents

# 17 - Diagnostic issues

Diagnostic issues

# 18 - Clinical guidance

# Clinical guidance

# 19 - Prescribing for anxiety disorders in children

# Prescribing for anxiety disorders in children and adolescents

582 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 5 Anxiety disorders in children and adolescents Diagnostic issues Fear and worry are common in children and they are part of normal development. At the same time, anxiety disorders often begin in childhood and adolescence1 and they are the most common psychiatric disorders in this age group, with overall prevalence between 8% and 30% depending on the impairment cut-offs used.2 Anxiety disorders may be even more common in children with neurodevelopmental disorders.3 In children, the more obvious clinical presentation with distress and avoidance may be masked by prominent behavioural symptoms (e.g. irritability and angry outbursts linked to avoidance). Therefore, the assessment and treatment of anxiety disorders in children need to be undertaken by clinicians who can discriminate normal, developmentally appropriate worries, fears and shyness from anxiety disorders that significantly impair a child’s functioning, and who can appreciate developmental variations in the presentation of symptoms. Clinical guidance Anxiety symptoms in children and adolescents often improve with age, presumably in parallel to the development of the prefrontal cortex and, in particular, executive function. However, anxiety disorders are distressing and impairing conditions that need to be treated promptly. Chronic stress mediators may have significant impact on brain development4 and functional impairment linked to anxiety symptoms may prevent young people from accessing normative experiences that are critical for social, emotional and cognitive development. Finally, early and effective treatment may prevent continuity of psychopathology into adulthood: for example, young people with anxiety disorders are three times more likely to have anxiety and depression in adult life compared with non-anxious youth.5 Guidelines for the treatment of anxiety disorders in children and adolescents have been made available in the UK and the USA. NICE guidelines focus on the treatment of social anxiety disorder in children and adolescents, suggesting the use of cognitive behavioural therapy and cautioning against the routine use of pharmacological treatment for social anxiety in this age group.6 Guidelines from AACAP cover the treatment of all anxiety disorders except post-traumatic

stress disorder (PTSD) and obsessive compulsive disorder (OCD) (which are classified separately according to DSM).7 AACAP guidelines suggest multimodal treatment including psychoeducation, psychotherapy (e.g. a 12-session course of exposure-based CBT) and pharmacotherapy. Drug treatment is endorsed for moderate-to-severe anxiety symptoms, when impairment makes participation in psychotherapy difficult, or when psychotherapy leads to only partial response. Prescribing for anxiety disorders in children and adolescents Before prescribing ■ ■Exclude other diagnoses: Anxiety symptoms can be mimicked by a range of psychiatric disorders including depression (inattention, sleep problems), bipolar disorder (irritability, sleep problems, restlessness), oppositional-defiant disorder (irritability,

Prescribing in children and adolescents CHAPTER 5 oppositional behaviour), psychotic disorders (social withdrawal, restlessness), ADHD (inattention, restlessness), autism spectrum disorder (social withdrawal, poor social skills, repetitive behaviours and routines) and learning disabilities. They may also be mimicked by a range of endocrine (hyperthyroidism, hypoglycaemia, phaeo-chromocytoma), neurological (migraine, seizures, delirium, brain tumours), cardiovascular (cardiac arrhythmias) and respiratory (asthma) conditions and lead intoxication. Anxiety-like symptoms can be observed in response to several drugs and substances including anti-asthma medications, sympathomimetics, steroids, SSRIs, antipsychotics (akathisia), diet pills, cold medicines, caffeine and energy drinks. ■ ■Beware contraindications to SSRIs and potential interactions. ■ ■Measure baseline severity: Use structured interviews including the Anxiety Disorders Interview Schedule (ADIS) and the Kiddie-Schedule for Affective Disorders and Schizophrenia (Kiddie-SADS); questionnaires including the Revised Children's Anxiety and Depression Scale (RCADS), Screen for Child Anxiety and Related Emotional Disorders (SCARED) or the Multidimensional Anxiety Scale for Children (MASC); and measures of functional impairment including the Children's Global Assessment Scale (CGAS). ■ ■Obtain consent: Discuss treatment with the young person and the family (e.g. name of medication, starting/estimated ending dose, titration timeline, possible side effects and strategies to monitor/minimise them, strategies to monitor progress, interventions for treatment-resistant cases). Document consent in writing. What to prescribe ■ ■SSRIs: These are the medications of choice for the treatment of anxiety disorders in children and adolescents. SSRI treatment is at least as effective as non-drug treatments.8 A 2019 meta-analysis identified seven short-term RCTs (<16 weeks; n treatment = 446, n control = 386) testing the efficacy of SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline) on changes in severity of anxiety in young people (Clinical Global Impression I [CGI-I] scale). The odds ratio (vs placebo) of overall treatment response was 4.6 (95%CI = 3.1–7.5) and, in anxiety symptoms specifically, 5.2 (95%CI = 2.8–8.8).9 The Childhood Anxiety Multimodal Study (CAMS) showed that monotherapy with sertraline (55% response) is as effective as CBT for anxiety (60% response) and better than placebo (24% response), and that combined therapy with sertraline and CBT is most likely to be successful (81% response).10 A 2017 network meta-analysis found that SSRIs significantly reduce clinician-reported and parent-reported (but not child-reported) anxiety symptoms and increased rates of remission.11 Another network meta-analysis found that the likelihood of treatment response was higher for SSRI compared with the following other medications;9 a standard meta-analysis showed that clinically significant treatment effects typically emerge by week 6 of treatment, and that SSRIs are associated with more rapid and greater improvement than these other medications.12 The most recent meta-analysis (11 studies, 2122 participants [2023])13 suggests broadly similar efficacy for SSRIs/ serotonin–noradrenaline reuptake inhibitors (SNRIs). With regard to tolerability, SSRIs are the best tolerated class of medications, particularly escitalopram and fluoxetine.14

 Sertraline, fluoxetine and fluvoxamine have been approved by the US FDA for treatment of paediatric OCD, and fluoxetine and escitalopram have been approved for treatment of paediatric depression. The FDA issued in 2004 a black box warning for concerns related to worsening of depression, agitation and suicidal ideation linked to SSRIs. These concerns were based on a review of studies of adolescents with depression rather than young people with anxiety. ■ ■SNRIs: Venlafaxine was tested in two short--term RCTs (n treatment = 294, n control = 311), duloxetine was tested in one short-term RCT (n treatment = 135, n control = 137) and atomoxetine was tested in one short-term RCT. The overall odds ratio of treatment response for SNRIs was 2.4 (95%CI = 1.7–3.6) over placebo.9 However, SNRIs did not show statistically significant effects on improvement in anxiety symptoms over placebo.9 The network meta-analysis mentioned earlier found that SNRIs significantly reduce clinician-reported (but not parent-reported or child-reported) anxiety symptoms.11 SSRIs are more effective and better tolerated9 so SNRIs could be considered a third-line treatment for anxiety disorders when two trials with different SSRIs prove ineffective. ■ ■Others: The 5HT1A agonist buspirone has been examined in one short-term RCT (n treatment = 334, n control = 225) and found not to be effective.15 The alpha2 agonist guanfacine was evaluated in one short-term RCT (n treatment = 62, n control = 21) and found to be associated with an increased odds ratio for treatment response (5.6 [95%CI = 1.4–26.8]) but not for improvement in anxiety symptoms.16 ■ ■Neither benzodiazepine nor tricyclic antidepressant use is supported by controlled trials in children.9 Benzodiazepine may also lead to paradoxical disinhibition in some children. Nevertheless, use of longer-acting benzodiazepines is at times considered in clinical practice either to alleviate disabling anxiety during initial titration of SSRIs or for rapid tranquillisation. Table 5.7 lists the doses for treating anxiety disorders in children and adolescents. After prescribing Acute phase ■ ■Start at the lowest available dose. ■ ■Monitor side effects. SSRIs are generally well tolerated during treatment for anxiety disorders in young people. Psychological side effects include worsening of anxiety symptoms, agitation and disinhibition. Physical side effects including gastrointestinal symptoms (e.g. nausea, vomiting, dyspepsia, abdominal pain, diarrhoea, constipation), headache, increased motor activity and insomnia may occur, often in mild and transient form. ■ ■After 1 week of treatment with SSRIs (2 weeks for SNRIs) when the child is compliant with medications and does not manifest more than minimal side effects, titrate incrementally with weekly intervals to the minimal therapeutic dose. ■ ■Monitor side effects and response (e.g. RCADS, SCARED, MASC, CGAS, CGI-I) frequently and systematically. ■ ■Dosage for treatment with SSRIs is often similar to dosage in adults because of faster metabolism in children. ■ ■Therapeutic effect should appear by 6–8 weeks of treatment. It is important to communicate this to families. ■ ■If partial or non-response, consider accuracy of diagnosis, adequacy of medication trial and compliance of patient.

 ■ ■To improve response, consider adding CBT, changing medication (e.g. switch SSRIs, other classes) or combining medications (e.g. for comorbidities, to treat side effects, to potentiate action). Augmentation strategies with buspirone, benzodiazepines, atypical antipsychotics and stimulant medications have been proposed but lack empirical support.7 Maintenance phase ■ ■Continue maintenance treatment for at least 1 year of stable improvement. ■ ■Monitor response and side effects regularly. Discontinuation phase ■ ■Because of lack of information on long-term safety and possible improvement in symptoms with age and learning, consider discontinuing treatment after a period of stable improvement. A trial of medication withdrawal should be started at a period of low stress/demands. Discontinuation should

also be considered if the medication is no longer working or the side effects are too severe. Taper SSRIs slowly (e.g. 25% of previous dose weekly) to minimise the risk of discontinuation symptoms. Monitor closely for recurrence of symptoms/relapse and, if deterioration is noted, consider restarting medication. Table 5.7 Typical dosage of medications for treatment of anxiety disorders in children and adolescents. Medication Starting dose (mg) Dose range (mg/day) SSRI Sertraline 12.-5–25 25–200 Fluoxetine 5–10 10–60 Fluvoxamine 12.5–25 50–200 (bd if >50) Paroxetine 5–10 10–-40 Citalopram* 5–10 10–40 SNRI Venlafaxine XR 37.5 37.5–225 Duloxetine 30–120 Alpha2 agonist Guanfacine 1–6 5HT1A partial agonist Buspirone* 5 tds 15–60 Benzodiazepine (prn) Clonazepam* 0.25–0.5 – Lorazepam* 0.5–1 – Note: always check dose with latest formal guidance, e.g. British National Formulary for Children (in the UK). *Treatments not supported by randomised controlled trial evidence. bd, twice daily; prn, as required; tds, three times daily.

# 20 - References

# References

586 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 5 Pre-school children Treatment of anxiety disorders in pre-school children must routinely focus on psychotherapy. In rare cases when a very young child has extreme ongoing symptoms and impairment, clinicians should reconsider diagnosis and case formulation, and reassess the adequacy of the psychotherapy trial. There are no RCTs of pharmacological interventions for anxiety in pre-school children, but case reports suggest a potential benefit of fluoxetine and buspirone.17 Any prescription in pre-school children is off-label.18 References


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# 21 - Obsessive compulsive disorder (OCD) and body

# Obsessive compulsive disorder (OCD) and body dysmorphic disorder (BDD) in children and adolescents

# 22 - Drug treatment in obsessive compulsive disord

# Drug treatment in obsessive compulsive disorder (OCD)

# 23 - Drug treatment in body dysmorphic disorder (B

# Drug treatment in body dysmorphic disorder (BDD)

Prescribing in children and adolescents CHAPTER 5 Obsessive compulsive disorder (OCD) and body dysmorphic disorder (BDD) in children and adolescents The treatment of OCD and BDD in children and young people largely follows the same principles as those for adults.1 BDD is recognised by both DSM-5 and ICD-11 as one of the obsessive compulsive disorders. Cognitive behavioural therapy is effective for both conditions in this age group and is recommended in the UK by NICE as the first-choice treatment, although it may be combined with medication for optimal effect.2 While CBT is the mainstay of treatment for OCD and BDD, medication alone may be the only viable therapeutic option in some cases. Some children are reluctant to engage with CBT, some may find it difficult to access or they may have very poor insight. This last situation may arise in the autism spectrum disorder alongside comorbid OCD or BDD. Insight in BDD is characteristically poorer than in OCD, with up to 50% of cases having beliefs about their appearance which are of delusional intensity. This too can affect motivation to engage with psychological therapy. Where medication is being used as the only evidence-based treatment, it is essential that this remains under review so that motivation and ability to engage with CBT are regularly revisited. Drug treatment in obsessive compulsive disorder (OCD) Sertraline (from age 6 years) and fluvoxamine (from age 8 years) are the SSRIs licensed in the UK for the treatment of OCD in young people. Studies have established the efficacy of SSRIs in the child and adolescent population in several placebo-controlled trials.3–5 SSRIs have a medium to large effect size in the treatment of OCD in children and young people.6 A meta-analysis of 12 RCTs of pharmacotherapy in young people under 19 years of age showed that medication is consistently more effective than placebo. Fluoxetine is the most efficacious SSRI for treatment of depression.7 Many young people presenting with OCD have a diagnosis of comorbid depression, so fluoxetine could be considered as an alternative SSRI to sertraline or fluvoxamine in these cases. Paroxetine is not recommended for use in children and young people. Clomipramine remains a useful drug for some individuals and is debatably more efficacious than the SSRIs in treating OCD in children and young people.8 However, clomipramine’s side effect profile (sedation, dry mouth, potential for cardiac side effects) tends to limit its use in this age group and, as a consequence, SSRIs remain the first-line choice in OCD. SNRIs are not recommended for treatment of OCD in children and young people, with no clear evidence of efficacy and poorer tolerability than SSRIs. Drug treatment in body dysmorphic disorder (BDD) No treatment is licensed in the UK for

either adults or children with BDD. However, evidence shows significant improvements with SSRIs, both in terms of BDD symptoms, suicidality and often comorbid depressive symptoms (80–90% of people with BDD also have a comorbid diagnosis of depression9). In the UK, NICE recommends fluoxetine as the SSRI of choice for treating BDD in children. Although BDD cases have delusional intensity beliefs about their appearance, antipsychotics are not effective and are

# 24 - Prescribing SSRIs in children

## Prescribing SSRIs in children

# 25 - NICE guidelines for the assessment and treatm

# NICE guidelines for the assessment and treatment of OCD and BDD

588 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 5 not recommended. Research in adult patients shows that BDD patients with delusional intensity appearance beliefs are as likely to respond to SSRI monotherapy as are non- delusional patients.9 Prescribing SSRIs in children In 2004, the UK MHRA cautioned against the use of SSRIs in children and young people owing to a possible increased risk of suicidal ideation.10 Careful re-analysis of treatment data suggests that SSRIs are clearly more efficacious in OCD than they are in moderate depressive episodes in children and young people.6 Investigators concluded that within the paediatric OCD group, the pooled risk for suicidal ideation and attempts was less than 1% across all studies. This of course is an important risk and should be explained and carefully monitored. Nonetheless, the naturalistic course of untreated OCD and BDD is that patients tend not to spontaneously remit, and they have tremendous associated morbidity. It is also known that untreated OCD and BDD are associated with a 10-fold increased risk of completed suicide compared with the general population in OCD.9,11 The risk of suicide in BDD is higher, with roughly one in three patients with BDD attempting suicide.12 These factors need to be carefully considered and discussed with the patient and their carers or family in making informed choices about treatment. On occasion, medications other than sertraline and fluvoxamine may be used ‘off-label’ with the appropriate and suitable cautions. NICE guidance13 for the treatment of OCD recommends the use of maximum tolerated dose strategies of two SSRIs before the use of clomipramine, owing to the latter drug’s greater propensity for side effects and need for cardiac monitoring. The alternative to clomipramine is augmentation with a low-dose antipsychotic. Factors guiding the choice of other medications may include issues such as the presence of other disorders; response to a certain drug in other family members; and cost and availability. Compliance with medication can be an issue with some young people, which can guide the choice of preparation. For instance, young people with poor compliance may be better suited to treatment with fluoxetine considering its long half-life compared with other SSRIs. A 2020 meta--analysis showed fluoxetine and sertraline to be more effective in OCD treatment than

fluvoxamine.8 Some children can find tablets or capsules hard to swallow and the availability of licensed liquid formulations is limited in most countries. NICE guidelines for the assessment and treatment of OCD and BDD NICE published guidelines in 2005 on evidence-based treatment options for OCD and BDD for young people and adults.13 NICE recommends a ‘stepped care’ model, with increasing intensity of treatment according to clinical severity and complexity.13 Assessment of the severity and impact of OCD or BDD can be aided by the use of the Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS) or BDD-YBOCS questionnaires, respectively, or other quantitative measures, both at baseline and as a helpful monitoring tool.14 The summary treatment algorithm from the NICE guideline is shown in Figure 5.1.

# 26 - Initiation of treatment with medication

# Initiation of treatment with medication

Prescribing in children and adolescents CHAPTER 5 Initiation of treatment with medication Clomipramine and SSRIs show a similar incremental effect on obsessions and compulsions from as early as 1–2 weeks after initiation and placebo-referenced improvements continue for at least 24 weeks. In some cases, a positive impact on mood may be seen before the initial changes in OCD symptoms.16 In the UK, NICE therefore recommends two treatment trials of SSRIs for OCD and BDD of 3 months and increasing towards the maximum tolerated effective dosage. Carefully explaining these temporal effects to patients can be important in sustaining compliance. In addition, the earliest signs of improvement may be apparent to an informant before the patient. Use of an observer- rated quantitative measure such as the CY-BOCS or BDD-YBOCS may therefore be helpful to monitor progress in clinical settings.17 Expert consensus typically suggests starting at the lowest dose known to be effective, titrating upwards and waiting for up to 12 weeks before evaluating effectiveness.18 Careful dose titration is particularly recommended if there is insufficient clinical response. In clinical practice a balance must clearly be struck between tolerability and the rate of dosage increase. It is worth noting that the majority of young people with OCD will require a higher dose of SSRI, and as such it may well be clinically indicated to increase the dose more quickly after starting an SSRI. Mild functional impairment Moderate or severe functional impairment Consider guided self-help support and information for family/carers Ineffective or refused Ineffective or refused Consider an SSRI (with careful monitoring) Multidisciplinary review Consider either (especially if previous good response to): Different SSRI Clomipramine SSRI + ongoing CBT (including ERP): Consider use in 8–11-year age group Offer to 12–18-year age group Carefully monitor for adverse events, especially at start of treatment Offer CBT (+ERP); involve family/carers (individual or group formats) Figure 5.1 Treatment options for children and young people with obsessive compulsive disorder. CBT, cognitive behaviour therapy; ERP, exposure and response prevention. Adapted from NICE guidance.13 Reprinted with permission.15

# 27 - Treatment refractory OCD and BDD in children

# Treatment-refractory OCD and BDD in children

590 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 5 Treatment-refractory OCD and BDD in children Evidence from randomised trials suggests that up to three-quarters of medicated patients have an adequate response to treatment. About a quarter of children and young people with OCD will therefore fail to respond to an initial SSRI, administered for at least 12 weeks at the maximum tolerated dose, in combination with an adequate trial of CBT and exposure and response prevention (ERP). These children should be reassessed and compliance clarified, and it should be ensured that clinical comorbidities are not being missed. In such cases, children and young people should usually have additional trials of at least one other SSRI. Research suggests that approximately 40% respond to a second SSRI in both OCD and BDD.19 Following this, if the response is limited, consideration should be given to referral to a specialist centre. In OCD, trials of clomipramine may be considered and/or augmentation with a low dose of risperidone or aripiprazole.13,20 Augmentation with antipsychotics is not recommended in the treatment of BDD. The combination of fluvoxamine and clomipramine has been used in refractory cases21,22 but, given the dangers of serotonin syndrome, these regimens should be reserved for specialist centres. Improved efficacy seems to be linked to the altering of the metabolism of clomipramine by fluvoxamine. There is evidence that low-dose antipsychotic augmentation of SSRI treatment as an off-label therapy can benefit patients whose response to treatment has been inadequate despite at least 3 months of two maximal tolerated separate SSRIs. There is a more robust evidence base in adult cohorts than in younger people. Only a third of treatment- resistant adult cases of OCD showed a meaningful response to this augmentation strategy. Small studies conducted on children and young people showed a clinical improvement for OCD, with a larger evidence base available for aripiprazole compared with risperidone.23–25 A 6–8-week trial of low-dose antipsychotic augmentation is typically sufficient to assess efficacy. In practice, doses no larger than aripiprazole 2.5–5mg daily or risperidone 0.5mg daily should be used. It is important to discontinue the anti psychotic if no response is noted after this trial of SSRI augmentation. Antipsychotics alone are not efficacious treatments for obsessive compulsive disorders. Often children and young people whose OCD or BDD has been difficult to treat have comorbidities such as autism spectrum disorder, ADHD or tic disorders. The response to medication can be differentially affected by these comorbidities. For instance, patients with tic disorders may benefit somewhat more from augmentation with

second- generation antipsychotics.26 Untreated ADHD can also commonly interfere with engagement with CBT due to poor focus. Very often efforts to address ADHD with appropriate treatments including medication can dramatically improve engagement with CBT. However, caution is required with regard to stimulant use, particularly for young people who are not ‘fighting back’ against compulsions. In this group, one can see an increase in compulsions as concentration improves. Careful clinical review and reformulation are important in treatment-resistant OCD and BDD. Comorbidities and wider psychosocial factors need to be considered for their impact on the treatment response overall. The evidence base around systemic factors and their application in OCD is poor. Very often clinical experience shows that it can be vital to support families and carers during treatment. Alternative experimental and adult treatments are given in Tables 5.8 and 5.9.

# 28 - Duration of treatment and long term follow up

# Duration of treatment and long-term follow-up

Prescribing in children and adolescents CHAPTER 5 Duration of treatment and long-term follow-up Untreated OCD runs a chronic course. A series of adult studies have shown that discontinuation of medication tends to result in a varying degree of symptomatic relapse.27 Some authors have suggested that those with comorbidities are at the greatest risk of relapse.28 Given that studies frequently exclude cases with additional comorbidities, it is likely that the relapse rates have been underestimated. In the UK, NICE guidelines recommend that if a young person has responded to medication, treatment for OCD or BDD should continue for at least 6 months after remission. This recommendation was based on clinical consensus rather than the product of carefully conducted research trials. Clinical experience would also suggest that when discontinuation of treatment is attempted it should be done slowly, cautiously and in a transparent manner with the patient and their family. Once again, the careful use of clinical outcome measures should be considered when stopping medication. There is a considerable evidence base and expert clinical consensus suggesting that discontinuing medication is associated with a deterioration in symptoms of either OCD or BDD. Increasingly adults and young people are being counselled to consider whether they wish to remain on SSRI medication longer term to mitigate the substantial risk of relapse of OCD or BDD symptoms. Thoughtful and honest discussion about the potential risks of stopping medication should be an active part of any care plan in OCD. Individuals with developmental disabilities often struggle to generalise the lessons taken from successful CBT. They also have a higher propensity for adverse effects such as activation syndromes with SSRIs, therefore titration may need to be slower.29 It is important that throughout childhood, adolescence and into adult life individuals with OCD or BDD should have rapid access to healthcare professionals, treatment opportunities and other support as needed. NICE recommends that if relapse occurs, people with OCD or BDD should be seen as soon as possible rather than placed on a routine waiting list because of the propensity for rapid deterioration of symptoms. Table 5.8 Alternative and experimental treatment of OCD in children and young people. Treatment Comment Aripiprazole augmentation of SSRI Evidence of clinical improvement in children and young people with OCD23,24,26,30 No evidence base for use in BDD Risperidone augmentation of SSRI Fewer studies than aripiprazole augmentation in children and young people25 Fluvoxamine with low-dose clomipramine Better tolerated than clomipramine monotherapy31 N-acetylcysteine (NAC) Limited evidence suggests children and adolescents with

OCD refractory to SSRIs or CBT may benefit from NAC augmentation.32 Memantine Limited evidence suggests potential benefit.33–35 Lamotrigine Case studies have reported response.36 BDD, body dysmorphic disorder; CBT, cognitive behavioural therapy; OCD, obsessive compulsive disorder.

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effective.39 Not to be used in female adolescents. High-dose SSRI (with ECG monitoring) Higher than licensed maximum dose SSRI associated with clinical improvement and well tolerated in a retrospective case note survey, double-blind trial and open-label study-40–42 SNRIs Duloxetine shown to be as effective as sertraline in a small RCT, and an open-label trial suggested it could reduce symptoms of OCD43,44 Mirtazapine Superior to placebo in an open trial45 Pregabalin Augmentation of sertraline was more effective than augmentation with placebo.46 5HT3 antagonists Ondansetron is effective as add-on treatment.47 Note risk of QT prolongation Ketamine IV Case report showed rapid resolution of symptoms48 Tolcapone (catechol-Omethyltransferase inhibitor) One small trial showed benefit over placebo.49 Methylphenidate Small study showed some benefit for OCD in combination with fluvoxamine50 Deep brain stimulation Could be effective treatment for resistant OCD.51 Transcranial magnetic stimulation (TMS) Meta-analysis showed that TMS can reduce the severity of OCD.52

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# 30 - Post traumatic stress disorder (PTSD) in chil

# Post-traumatic stress disorder (PTSD) in children and adolescents

Prescribing in children and adolescents CHAPTER 5 Post-traumatic stress disorder (PTSD) in children and adolescents Diagnostic issues Traumatic events and PTSD are common in young people. One in three children experiences traumatic events1 and about 1 in 13 children develops PTSD before age 18.1 The prevalence of PTSD in adolescents can be much higher in at-risk groups, for example those attending emergency departments, in forensic settings or among refugee/asylum seekers. Young people with PTSD are at high risk of self-harm (nearly 50%) and suicide attempt (20%) and are often functionally impaired, for example not being in education, employment or education (NEET) (more than 25%).1 Of note, more than three out of four young people with PTSD have comorbid psychiatric diagnoses, most commonly depression, conduct disorder, alcohol dependence or generalised anxiety disorder.1 Furthermore, PTSD is not the most common diagnosis in trauma-exposed young people – disorders that are most prevalent in the general population (e.g. depression, conduct disorder, alcohol dependence) are also more prevalent in trauma-exposed young people.1 A diagnosis of PTSD is based on the triad of intrusive re-experiencing, avoidance of stimuli associated with the trauma and hyper-arousal after trauma exposure. Because of the abnormal processing of traumatic memories, young people with PTSD may suffer persistent re-experiencing of the traumatic event(s) through nightmares or unwanted and distressing memories, which are often experienced as if they were happening in the ‘here and now’ and often do not appear as frank dissociative symptoms or flashbacks. In order to minimise re-experiencing symptoms, young people with PTSD often develop overt or covert avoidance strategies, keeping themselves busy or distracted or staying away from people or places that remind them of the traumatic event. As a result of the symptoms, young people with PTSD often feel under continued threat and, therefore, display physiological hyper-arousal, appearing alert and vigilant for danger, irritable and struggling to concentrate on daily tasks. Because of the varied clinical manifestations, the assessment and treatment of PTSD in children and adolescents should be undertaken by clinicians who have expertise in the clinical presentations seen in trauma-

exposed children and can appreciate developmental variations in the manifestation of symptoms. Clinical guidance The UK NICE guidelines2 advise that treatment of PTSD in young people should focus on psychotherapy, with 12 sessions of trauma-focused CBT (TF-CBT) for PTSD resulting from a single traumatic event or longer for chronic or recurrent events. If TF-CBT is not effective, or based on the young person’s preference, treatment may also include eye movement desensitisation and reprocessing (EMDR). Based on the current evidence in NICE guidelines,2 the AACAP3 and the International Society for Traumatic Stress Studies (ISTSS),4 pharmacotherapy is not recommended for treatment of PTSD in young people. The evidence for efficacy of pharmacotherapy (SSRIs and SGAs) in adults is also somewhat limited at present.5,6 However, because of the high rates of comorbidity,1 pharmacotherapy may be needed to target co-occurring psychiatric disorders. In adult PTSD, the best supported treatments are fluoxetine, paroxetine and

# 31 - References

## References

# 32 - Diagnostic issues

# Diagnostic issues

# 33 - Clinical guidance

# Clinical guidance

Prescribing in children and adolescents CHAPTER 5 Post-traumatic stress disorder (PTSD) in children and adolescents Diagnostic issues Traumatic events and PTSD are common in young people. One in three children experiences traumatic events1 and about 1 in 13 children develops PTSD before age 18.1 The prevalence of PTSD in adolescents can be much higher in at-risk groups, for example those attending emergency departments, in forensic settings or among refugee/asylum seekers. Young people with PTSD are at high risk of self-harm (nearly 50%) and suicide attempt (20%) and are often functionally impaired, for example not being in education, employment or education (NEET) (more than 25%).1 Of note, more than three out of four young people with PTSD have comorbid psychiatric diagnoses, most commonly depression, conduct disorder, alcohol dependence or generalised anxiety disorder.1 Furthermore, PTSD is not the most common diagnosis in trauma-exposed young people – disorders that are most prevalent in the general population (e.g. depression, conduct disorder, alcohol dependence) are also more prevalent in trauma-exposed young people.1 A diagnosis of PTSD is based on the triad of intrusive re-experiencing, avoidance of stimuli associated with the trauma and hyper-arousal after trauma exposure. Because of the abnormal processing of traumatic memories, young people with PTSD may suffer persistent re-experiencing of the traumatic event(s) through nightmares or unwanted and distressing memories, which are often experienced as if they were happening in the ‘here and now’ and often do not appear as frank dissociative symptoms or flashbacks. In order to minimise re-experiencing symptoms, young people with PTSD often develop overt or covert avoidance strategies, keeping themselves busy or distracted or staying away from people or places that remind them of the traumatic event. As a result of the symptoms, young people with PTSD often feel under continued threat and, therefore, display physiological hyper-arousal, appearing alert and vigilant for danger, irritable and struggling to concentrate on daily tasks. Because of the varied clinical manifestations, the assessment and treatment of PTSD in children and adolescents should be undertaken by clinicians who have expertise in the clinical presentations seen in trauma-exposed children and can appreciate developmental variations in the manifestation of symptoms. Clinical guidance The UK NICE guidelines2 advise that treatment of PTSD in young people should focus on psychotherapy, with 12 sessions of trauma-focused CBT (TF-CBT) for PTSD resulting from a single traumatic event or longer for chronic or recurrent events. If TF-CBT is not effective, or based on the young person’s preference, treatment may also include eye movement desensitisation and reprocessing (EMDR). Based on the current evidence in NICE guidelines,2 the AACAP3 and the International Society for Traumatic Stress Studies (ISTSS),4 pharmacotherapy is not recommended for treatment of PTSD in young people. The evidence for efficacy of pharmacotherapy (SSRIs and SGAs) in adults is also somewhat limited at present.5,6 However, because of the high rates of comorbidity,1 pharmacotherapy may be needed to target co-occurring psychiatric disorders. In adult PTSD, the best supported treatments are fluoxetine, paroxetine and

596 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 5 venlafaxine.7 3,4-Methylenedioxymethamphetamine (MDMA),8 ketamine9 and psychedelic drugs10 also show promise. Prazosin appears to be effective in reducing PTSD-related nightmares in children aged 4–-18 years.11 None of these agents is currently used to any extent in children and adolescents.

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# 34 - Attention deficit hyperactivity disorder (ADH

# 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.

# 35 - References

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# 36 - Autism spectrum disorder (ASD) in children an

# Autism spectrum disorder (ASD) in children and adolescents

# 37 - Pharmacological treatment of core ASD symptom

# Pharmacological treatment of core ASD symptoms

Prescribing in children and adolescents CHAPTER 5 Autism spectrum disorder (ASD) in children and adolescents Autism spectrum disorder is a complex condition characterised by core deficits in social communication development and behaviour (stereotypies and/or restricted and unusual patterns of interests) as well as sensory difficulties. ICD-11 now matches DSM-5 in removing the subtypes of autism (e.g. the term Asperger's syndrome has been discontinued). In addition, ICD-11 distinguishes between ASD with or without intellectual development. DSM-5 recommends recording whether or not there is accompanying intellectual impairment. The heterogeneity of ASD poses assessment and treatment challenges. Co-occurring mental health conditions are highly prevalent in ASD1 with 69–79% of individuals experiencing at least one in their lifetime.2,3 These include attention deficit hyperactivity disorder (ADHD), disruptive behavioural disorders, anxiety and obsessive compulsive and mood disorders. Other associated problems include intellectual disability, epilepsy, sleep disturbance, self-harm, irritability and aggression towards others. Associated neurodevelopmental, medical and psychiatric disorders complicate the symptom profile and affect overall outcome. Evaluating and optimally treating co-occurring conditions and/or associated problem behaviours are, therefore, essential. Currently there are no validated or licensed pharmacological treatments that alleviate core ASD symptoms.4,5 Targeting problem behaviours and comorbid psychiatric conditions with pharmacological interventions is, however, common practice. Pharmacotherapies are commonly used in individuals with ASD as adjuncts to psychological interventions. The evidence to date4,6 shows reasonable efficacy of risperidone and aripiprazole for irritability and aggression; supports the use of methylphenidate, atomoxetine and guanfacine for ADHD and melatonin for sleep problems; but shows limited efficacy of SSRIs for anxiety, depression and repetitive behaviours. The evidence for antiepileptics remains inconsistent. There is a potential role for α2 agonists, cholinergic agonists, glutamatergic agents, gamma--aminobutyric acid (GABA) agonists and oxytocin but these require further investigation.4,6 Individuals with ASD are likely to experience more severe adverse effects than typically developing

individuals.4–6 Therefore, achieving an effective dose with minimum adverse effects can be a challenging task. Treatment should be initiated in small doses and increased about every five half--lives of the drug, and it may take 4–6 weeks of titration to determine the therapeutic dose for each individual case.7 Excluding any medical conditions, the presence of pain or any other physical discomfort such as gastro-esophageal reflux must be a priority before managing problem behaviour with psychotropic drugs. A comprehensive physical examination should be part of standard practice. The efficacy and adverse effects associated with pharmacotherapy in individuals with ASD should be systematically monitored in view of their impaired communication and the increased propensity for more adverse effects. Standardised behaviour rating scales and adverse effect checklists are essential tools in monitoring progress.8 Pharmacological treatment of core ASD symptoms Evidence from clinical trials to date has not demonstrated clear efficacy of any psychotropic agent in routinely treating core symptoms of ASD.4,6

606 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 5 Restricted repetitive behaviours and interests (RRBIs) RRBIs are distressing and disruptive to functioning and therefore an important treatment target to improve overall outcomes in ASD.9 Behavioural therapies should be used as first line. When RRBIs are severe with significant impact on functioning and/or pose risks to others or self then pharmacotherapy can be considered. A Cochrane review (last updated in 2013) found ‘no evidence of effect of SSRIs on reducing RRBIs in children and emerging evidence of harm’ although there are data that support their use in adults.10 A 2022 meta-analysis of 16 studies demonstrated a small effect size for antidepressants in treating restricted and repetitive behaviours. Subgroup analyses indicated that clomipramine had a higher efficacy than SSRIs and adults had a better response than adolescents and children.11 Risperidone is probably effective in reducing RRBIs in children who have high levels of irritability or aggression12 (any specific efficacy for repetitive behaviours is doubtful). Reductions in stereotypical behaviours have also been -reported13–16 albeit in studies with methodological limitations.6 A 2020 meta-analysis of studies on a wide range of currently available pharmacological agents showed evidence supporting only antipsychotic medication,17 whereas another recent meta-analysis of nine studies found no evidence for any pharmacological agent in reducing RRBIs.18 Overall, given the profile of adverse effects of dopamine-blocking agents, consensus guidance from the British Association for Psychopharmacology6 rightly cautions against their routine use for the treatment of RRBIs. If they are used, they should be prescribed in small doses and as part of a carefully considered, time--limited and monitored overall treatment plan. Social and communication impairment Currently, no drug has been consistently shown to improve the core social and communication impairments in ASD.7 Risperidone may have a secondary effect through improvement in irritability.19 Analysis of data from two multicentre trials suggested that risperidone was effective for the treatment of social disability in children with ASD.20 Glutamatergic drugs and oxytocin looked promising.21 However, two meta-analyses and two recent double-blind placebo-controlled trials suggested that oxytocin has no significant effect on social communication.22–25 Larger studies with better methodology are needed.23,26 Sulforaphane has shown mixed results with both positive and negative trials.27–-29 Insulin growth factor 1 (IGF-1)30 awaits further work to prove its efficacy in modifying ASD core symptoms, as do glutamatergic agents.31–33 Acetylcysteine34 is probably not effective. Three small double-blind placebo-controlled trials using folinic acid for language impairment look encouraging.35 There is growing but inconsistent evidence for dietary interventions reducing ASD core symptoms.36,37 The targeting of the gut microbiome, including probiotic treatment and faecal microbiota transplants, has drawn much interest.38 However, there is little evidence to

support the use of nutritional supplements or dietary therapies for children with ASD36 or indeed any relationship between maternal food intake and child’s diet and the development of ASD/symptoms severity.37

# 38 - Pharmacological treatment of co occurring dis

# Pharmacological treatment of co-occurring disorders and problem behaviours in ASD

Prescribing in children and adolescents CHAPTER 5 Pharmacological treatment of co-occurring disorders and problem behaviours in ASD Inattention, overactivity and impulsiveness in ASD (symptoms of ADHD) Individuals with ASD have high rates of inattention, overactivity and impulsiveness and in around a third of patients these symptoms merit the diagnosis of ADHD.1,39 The largest controlled trial to date has been with methylphenidate, conducted by the Research Units on Paediatric Psychopharmacology (RUPP) Autism Network.40,41 In a previous retrospective and prospective study of children with ASD, Santosh and colleagues42 reported positive benefits of treatment with methylphenidate. In general, methylphenidate produces highly variable responses in children with ASD and ADHD symptoms, ranging from marked improvement with few adverse effects to poor response with or without problematic adverse effects. A large double-blind placebo-controlled trial of methylphenidate in children with intellectual disability and ADHD showed that optimal dosing with methylphenidate was effective in some.43 Adverse effects are more commonly reported than in children with ADHD alone.44–46 However, where ADHD symptoms are severe and/or disabling, it is reasonable to proceed with a treatment trial of methylphenidate. It is advisable to warn parents of the lower likelihood of response and the potential adverse effects and to proceed with low initial doses (around 0.125mg/kg three times daily, depending on the preparation) increasing by small increments. Treatment should be stopped immediately if behaviour deteriorates or there are unacceptable adverse effects. A systematic review6 confirms that, although effective, the efficacy of methylphenidate for treatment of ADHD in ASD is less than in ADHD alone and that more adverse effects (decreased appetite, sleeping difficulties, abdominal discomfort, social withdrawal, irritability and emotional outbursts) should be expected in ASD. A 2021 meta-analysis supports the efficacy of methylphenidate and atomoxetine.47 There are no

published data on the efficacy of amfetamines in children with ASD even though they have been used to treat ADHD in these patients as well as in typically developed children. Lisdexamfetamine (a pro-drug containing d-amfetamine bound to amino acid lysine) has been found to have efficacy and tolerability in treating ADHD in children and young people48 but with no specific data about those with ASD. Atomoxetine is a noradrenergic reuptake inhibitor licensed to treat ADHD with similar efficacy to methylphenidate.6 Preliminary evidence from small open-label trials and a handful of randomised double-blind trials49,50 showed that it may be useful in children with ASD, with the most common adverse effects being nausea, fatigue and sleep difficulties. These studies were followed by a larger trial that confirmed that atomoxetine (alone and combined with parent training) significantly reduced ADHD symptoms.51 In a 24-week extension of the same study, atomoxetine combined with parent training was superior in reducing ADHD symptoms to atomoxetine alone.52 There is evidence that α2 agonists (clonidine and guanfacine) can be used as alternative treatments. A multisite RCT of extended-release guanfacine compared with placebo in children with ASD (mean age 8.5 years) over a period of 8 weeks showed that it is safe and effective in managing hyperactivity in this group.53 No serious adverse events except for drowsiness, fatigue and decreased appetite were reported.

608 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 5 There are reports from controlled studies supporting the use of risperidone or aripiprazole for ADHD symptoms. However, these were not primary outcomes of the studies and therefore need further investigation. Irritability (aggression, self-injurious behaviour, severe disruptive behaviours) Aggression towards others and self, frequently underlined by irritability, is a common problem in ASD. Although behavioural and environmental approaches should be first- line treatments, more severe and dangerous behaviours usually necessitate pharmacotherapy.54 The duration of recommended treatment is difficult to derive from published evidence but treatment appears to be beneficial for up to 6–12 months.55 Efforts to reduce and possibly discontinue such treatment at the end of this period should be strongly considered.54,55 SGAs are the first-line pharmacological treatment for children and adolescents with ASD and associated irritability.55–58 Risperidone59,60 and aripiprazole61 have been reliably shown to help with irritability and associated disruptive behaviours5 in ASD and have been approved for this use by the US FDA. In a meta-analysis of data from 46 RCTs62 comparing efficacy of risperidone, aripiprazole and other compounds with placebo, risperidone and aripiprazole were the most effective, with moderate to large effect sizes. Another meta- analysis of short-term (8 weeks) aripiprazole in the treatment of irritability in ASD children aged 6–17 years63 found similar results when compared with placebo. The most recent Cochrane review64 concluded that aripiprazole and risperidone probably reduce both irritability and self-injury with a large effect size. However, no effect was shown for aggression. The usual recommended dose of aripiprazole for maintenance is between 5 and 15mg daily.55 The starting dose is 2mg/day. The dosing of risperidone is rather more complicated – FDA-recommended dosages for risperidone are outlined in Box 5.2. Despite their promising efficacy, adverse effects such as weight gain and metabolic changes, increased appetite and somnolence (even with aripiprazole) can be problematic.16,65–68 Research is underway to determine if therapeutic drug monitoring of risperidone and aripiprazole will help in optimising treatment while minimising weight gain.69 One long-term placebo discontinuation study found that relapse rates did not differ between those who stayed on aripiprazole versus those randomised to switch to only placebo, suggesting that re-evaluation of aripiprazole use after a period of stabilisation in irritability symptoms is warranted.70 There is only one study that makes a direct head-to-head comparison71 showing similar tolerability and efficacy

profiles for risperidone and aripiprazole. Risperidone usually causes hyperprolactinaemia which, although it may be asymptomatic, may have longer-term effects, therefore necessitating close monitoring. Aripiprazole has no effect on prolactin, which makes it a preferred option. Aripiprazole may on the other hand be ineffective for self-injurious behaviours.6 Lurasidone, in fixed doses of 20 or 60mg/day, has been shown to be ineffective in a randomised double-blind trial over 6 weeks.72 The effectiveness of other SGAs such as olanzapine,73 quetiapine, ziprasidone and clozapine has not been tested in adequately powered RCTs. While controlled studies support the use of mood stabilisers such as lithium74,75 and sodium valproate76 in the treatment of persistent aggression in children they are not as effective as SGAs for the treatment of irritability in ASD.77 Limited data support the combination of risperidone and topiramate being better than risperidone alone.78 Further RCTs are probably warranted of brain-derived neurotrophic factor stimulators such as loxapine and amitriptyline.79

Prescribing in children and adolescents CHAPTER 5 Use of risperidone in children and adolescents Box 5.2 US Food and Drug Administration guidance for risperidone dosing in children and adolescents80 ■ ■Risperidone is indicated for the treatment of irritability associated with autistic spectrum disorder (ASD) in children (aged 5 years and over) and adolescents in the UK/EU and USA ■ ■The dosage of risperidone should be individualised according to the response of the patient Doses of risperidone in paediatric patients with autism spectrum disorders (by total mg/day) Weight categories Days 1–3 Days 4–18 Increments if dose increases are needed Dose range <20kg* 0.25mg 0.5mg +0.25mg at ≥2-week intervals 0.5–3mg† ≥20kg 0.5mg 1.0mg +0.5mg at ≥2-week intervals 1.0–3mg‡ *Caution should be exercised for children <15kg – no dosing data available †Therapeutic effect plateaus at 1mg/day ‡Those weighing >45kg may require higher - doses – therapeutic effect plateaus at 3mg General considerations ■ ■Risperidone can be administered once daily or twice daily ■ ■Patients experiencing somnolence may benefit from taking the whole daily dose at bedtime ■ ■Once sufficient clinical response has been achieved and maintained, consideration may be given to gradually lowering the dose to achieve the optimal balance of efficacy and safety ■ ■There is insufficient evidence from controlled trials to indicate how long treatment should continue Adverse effects ■ ■Weight gain, somnolence and hyperglycaemia require monitoring ■ ■Long-term safety of risperidone in children and adolescents with ASD remains to be fully determined Using benzodiazepines to manage irritability and aggression in ASD is not recommended. However, it may be necessary to manage acute aggression with a benzodiazepine. The possibility of behavioural disinhibition that may worsen aggression must be borne in mind. The use of minocycline, arbaclofen or amantadine for irritability is not recommended unless better evidence from double-blind RCTs is available.6 Sleep disturbance Children with ASD have significant sleep problems,81 with sleep-onset insomnia, sleep-maintenance insomnia and irregularities of the sleep–wake cycle being the typical problems encountered. It is essential to understand the aetiology of the sleep problem before embarking on a course of treatment. Abnormalities in the melatonin system have received some attention.82

610 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 5 Melatonin has been shown in 17 studies to be beneficial in children with ASD.83 A meta-analysis of five studies showed good efficacy with doses ranging from 1mg to 10mg and treatment lasting from 14 days to over 4 years.84 Melatonin is usually very well tolerated.84,85 One RCT showed that, while melatonin improved sleep onset, the child’s behaviour during the day did not improve.86 There is also evidence that melatonin combined with CBT is superior to melatonin only, CBT only and placebo in

reducing symptoms of insomnia.87 Risperidone may benefit sleep difficulties in those with extreme irritability. In the anxious or depressed child, antidepressants may be beneficial. Insomnia due to hyper arousal may benefit from clonidine or clonazepam.88 Anxiety, OCD and depression SSRIs have yet to show specific efficacy in ASD. Preliminary data from a randomised placebo-blind clinical trial showed beneficial effects of fluoxetine in reducing OCD symptoms in children with ASD, although confounding factors precluded firm conclusions.89 In a systematic review,6 although risperidone was reported by several studies to reduce OCD and anxiety symptoms in young people with ASD, the selection of participants with high levels of irritability did not allow firm conclusions to be drawn about specific effects of risperidone on OCD and anxiety. There is little or no evidence for treating anxiety or OCD symptoms with risperidone, clomipramine or an SSRI. There are some data on buspirone effectively targeting anxiety in ASD90 and propranolol showing positive cognitive effects in ASD.91 However, further evaluation is needed. Guidance on doses of fluoxetine can be found in Box 5.3. Use of fluoxetine in children and adolescents When using fluoxetine to treat repetitive behaviours in ASD patients, doses much lower than those used to treat depression are normally required. It is advisable to use a liquid preparation and begin at the lowest possible dose, monitoring for adverse effects. A suitable regimen is outlined in Box 5.3. Box 5.3 Use of fluoxetine in children and adolescents ■ ■Liquid fluoxetine (as hydrochloride): 20mg/5mL ■ ■2.5mg/day a day for 1 week; note that 2.5mg = 0.625mL, which is difficult to measure accurately ■ ■Follow with a flexible titration schedule based on weight, tolerability and adverse effects up to a maximum dose of 0.8mg/kg/day (0.3mg/kg/day for week 2, 0.5mg/kg/day for week 3 and 0.8mg/kg/day subsequently) ■ ■Reduction may be indicated if adverse effects are problematic Adverse effects ■ ■Monitor for treatment-emergent suicidal behaviour, self-harm and hostility, particularly at the beginning of treatment ■ ■Hyponatraemia is also possible – see Chapter 3

# 39 - References

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# 40 - Tics and Tourettes syndrome in children and a

# Tics and Tourette’s syndrome in children and adolescents

# 41 - Detection and treatment of comorbidity

## Detection and treatment of comorbidity

# 42 - Education and behavioural treatments

Education andÂ behavioural treatments

# 43 - Pharmacological treatments

# Pharmacological treatments

614 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 5 Tics and Tourette’s syndrome in children and adolescents Transient tics occur in 5–20% of children. Tourette’s syndrome (TS) occurs in about 0.7% of children and adolescents and is defined by persistent motor and vocal tics. As many as 65% of individuals with TS will have no tics or only very mild tics by adult life. Tics wax and wane over time and are variably exacerbated by external factors such as stress, inactivity and fatigue, depending on the individual. Tics are about two to three times more common in boys than girls.1 Functional tic disorders (involuntary physical movements, often related to anxiety) have also been described in recent years.2 These are typically seen in teenage girls. Detection and treatment of comorbidity Comorbid OCD, ADHD, ASD, depression, anxiety and behavioural problems are more prevalent than would be expected by chance, and often cause the major impairment in people with tic disorders.3 These comorbid conditions are usually treated first before assessing the level of disability caused by the tics. Education and behavioural treatments Most people with tics do not require pharmacological treatment. Education is crucial for the individual with tics, their family and the people they interact with, especially at school (Figure 5.2). Treatment aimed primarily at reducing tics is warranted if the tics cause distress to the patient or are functionally disabling. Behavioural interventions have been found to be effective with similar effect sizes to antipsychotic medication.4,5 Habit reversal, comprehensive behavioural intervention for tics and exposure and response prevention are the behavioural treatments of choice.6 Pharmacological treatments Studies of pharmacological interventions in TS are difficult to interpret for several reasons: ■ ■There is a large inter-individual variation in tic frequency and severity. Small, randomised studies may include patients who are very different at baseline. ■ ■The severity of tics in a given individual varies markedly over time, making it difficult to separate drug effect from natural variation. ■ ■The bulk of the literature consists of case reports, case series, open studies and underpowered, randomised studies. Publication bias is also likely to be an issue. ■ ■A high proportion of patients have comorbid psychiatric illness. It can be difficult to disentangle any direct effect on tics from an effect on the comorbid illness. This makes it difficult to interpret studies that report improvements in global functioning rather than specific reductions in tics. ■ ■Large numbers of individuals attending clinics with TS appear to use complementary or alternative therapies, with the majority reporting benefits and up to half finding

# 44 - Adrenergic 2 agonists

## Adrenergic 2 agonists

# 45 - Antipsychotics

# Antipsychotics

Prescribing in children and adolescents CHAPTER 5 these more helpful compared with medication.7 Robust research about the use of complementary or alternative therapies, their efficacy and potential adverse effects is lacking8 and certainty of evidence for their use is very low.9 Adrenergic α2 agonists Clonidine has been shown in open studies to reduce the severity and frequency of tics but in one study this effect did not seem to be convincingly larger than placebo.10 Other studies have shown more substantial reductions in tics.11–14 Therapeutic doses of clonidine are in the order of 3–5mcg/kg, and the dose should be built up gradually. A transdermal patch has also shown effectiveness.15 The main adverse effects are sedation, postural hypotension and depression. Patients and their families should be informed not to stop clonidine suddenly because of the risk of rebound hypertension. Guanfacine also has some evidence of effectiveness in the treatment of tics.16,17 The efficacy of clonidine (but not of guanfacine) was demonstrated in a 2023 systematic review and network meta-analysis of double-blind RCTs in TS which included children, adolescents and adults.9 Adrenergic α2 agonists may also be used in children with ADHD whose tics deteriorate with stimulant medication.18 Antipsychotics Adverse effects of antipsychotics may outweigh their beneficial effects in the treatment of tics so it is recommended that clonidine or guanfacine is generally tried first (Figure 5.2). Antipsychotics may, however, be more effective than adrenergic α2 agonists in alleviating tics.9 A number of first-generation antipsychotics have been used in TS. In a Cochrane review, pimozide demonstrated robust efficacy in a meta-analysis of six trials.19 In these trials, pimozide was compared with haloperidol (one trial), placebo (one trial), haloperidol and placebo (two trials) and risperidone (two trials) and was found to be more effective than placebo, as effective as risperidone and slightly less effective than haloperidol in reducing tics. It was associated with less severe adverse effects than haloperidol but did not differ from risperidone in that respect. ECG monitoring is essential for pimozide and haloperidol. Haloperidol is often poorly tolerated. Tiapride may also be effective, but evidence may not be generalisable and it has limited availability.9 SGAs, in particular aripiprazole, have in recent years been used more commonly for the treatment of TS.20 Aripiprazole is an effective and well-tolerated treatment of children with TS (and also tics21). A 10-week multicentre double-blind randomised placebo-controlled trial (N = 61) demonstrated the efficacy of aripiprazole in tic reduction in TS. Treatment was associated with significantly decreased serum prolactin concentration, increased mean body weight (by 1.6kg), body mass index and waist circumference.22 Aripiprazole was also found to be effective in another randomised double-blind placebo-controlled trial (N = 133) comparing low-dose aripiprazole (5mg/day if <50kg; 10mg/day if ≥50kg), high-dose aripiprazole (10mg/day if <50kg; 20mg/day if ≥50kg) or placebo for 8 weeks.23 At week 8, tics were reduced in both the high-dose group and the low-dose group, with 69% of patients in the low-dose group and 74% in the high-dose group being very much improved or much improved, compared with 38% in the

# 46 - Other drugs

# Other drugs

616 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 5 placebo group. Surprisingly, a higher proportion of children in the low-dose group (18.2%) compared with the high-dose group (9.3%) and placebo group (9.1%) gained clinically significant weight (≥7%) which may have been related to a lower average baseline weight in this group. Several case series also support the use of aripiprazole.24–27 A study evaluating the metabolic side effects of aripiprazole (N = 25) and pimozide (N = 25) in TS over a 24-month period demonstrated that treatment was not associated with significant increase in body mass index. However, pimozide treatment was associated with increases in blood glucose that did not plateau from 12 to 24 months, aripiprazole treatment was associated with increased cholesterol and both medications were associated with increased triglycerides.28 Two meta-analyses support the efficacy of aripiprazole.29,30 One study31 suggests twice-weekly administration may be better tolerated than daily dosing. A small RCT (N = 24) comparing aripiprazole with sodium valproate in children with TS demonstrated a statistically significant difference in tic reduction favouring aripiprazole.32 Risperidone has, in addition to the studies mentioned, also been shown to be more effective than placebo in a small (N = 34) randomised study.33 Fatigue and increased appetite were problematic in the risperidone arm and a mean weight gain of 2.8kg over 8 weeks was reported. One small RCT found risperidone and clonidine to be equally effective.34 A small double-blind crossover study suggested that olanzapine35 may be more effective than pimozide. Sulpiride has been shown to be effective and relatively well tolerated,36 as has ziprasidone.37 Open studies support the efficacy of quetiapine38 and olanzapine.39,40 One very small crossover study (N = 7) found no effect for clozapine.41 Antipsychotic medications may not differ from each other in terms of efficacy for tics, with low to very low certainty of evidence for this comparison.9 Overall, metabolic side effects and weight gain are common with second-generation antipsychotics, even aripiprazole, so benefit/risk ratios need careful discussion.42 Other drugs A small, double-blind placebo-controlled crossover trial of baclofen was suggestive of beneficial effects in overall impairment rather than a specific effect on tics.43 The numerical benefits shown in this study did not reach statistical significance. Similarly, a double-blind placebo-controlled trial of nicotine augmentation of haloperidol found beneficial effects in overall impairment rather than a specific effect on tics.44 These benefits persisted for several weeks after nicotine (in the form of patches) was withdrawn. Nicotine patches were associated with a high prevalence of nausea and vomiting (71% and 40%, respectively). The authors suggest that use as required may be appropriate. Flutamide, an antiandrogen, has been the subject of a small RCT in adults with TS. Modest, short-lived effects were seen in motor but not phonic tics.45 A small RCT showed significant advantages for metoclopramide over placebo46 and for topiramate over placebo. A meta-analysis identified 14 RCTs (all from China) comparing topiramate with haloperidol or tiapride. It concluded that owing to the overall low quality of the study designs, there is not enough evidence to support the routine use of topiramate in clinical

practice.47 Tetrabenazine may be useful as an add-on treatment.48 Ecopipam, a D1 receptor antagonist, was also found to be effective in the treatment of tics in a

Prescribing in children and adolescents CHAPTER 5 randomised placebo-controlled crossover study including children and adolescents with TS.49 A second trial (n = 153)50 confirmed the efficacy of ecopipam. The monoamine depleting agents deutetrabenazine and valbenazine, the selective serotonin 5-HT3 receptor antagonist ondansetron and pergolide, a D1-D2-D3 agonist, are probably not effective.9,51 Case reports or case series describing positive effects have been published for - clomiphene,52 tramadol,53 ketanserin,54 cyproterone,55 levetiracetam,56 pregabalin57 and cannabis.58 A Cochrane review of cannabinoids concluded that there was little if any current evidence for efficacy59 and, despite a strong biological rationale for use, their overall efficacy and safety remain largely unknown.60 Many other drugs have been reported to be effective in single case reports. Patients in these reports all had comorbid psychiatric illness, making it difficult to determine the effect of these drugs on TS alone. Botulinum toxin has been used to treat bothersome or painful focal motor tics, particularly those affecting neck muscles.42 However, a 2018 Cochrane review expressed uncertainty about its place in the treatment of tics owing to the low quality of available evidence.61 There may be a subgroup of children who develop tics and/or OCD in association with streptococcal or other infections or triggers. This group has been given (in the case of Streptococcus) the acronym PANDAS (paediatric autoimmune neuropsychiatric disorder associated with Streptococcus)62 or, more broadly, PANS (paediatric acute- onset neuropsychiatric syndrome).63 This is thought to be an autoimmune-mediated effect, and there have been trials of immune-modulatory therapy in these children as well as treatment with antibiotics for active infections and also as preventative treatment. More research in this area is warranted. *It is extremely rare in practice to get to this point – almost all cases can be effectively treated by recommendations above this point. Not fully effective Poorly tolerated Not effective* Educational and behavioural treatment Clonidine or guanfacine Antipsychotic treatment, e.g. aripiprazole or risperidone Consider older or more experimental treatments (see text) Not fully effective Figure 5.2 Summary of recommendations for the treatment of tics and Tourette’s syndrome.

# 47 - References

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# 48 - Melatonin in the treatment of insomnia in chi

# Melatonin in the treatment of insomnia in children and adolescents

# 49 - Efficacy

# Efficacy

620 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 5 Melatonin in the treatment of insomnia in children and adolescents Insomnia is a common symptom in childhood. Underlying causes may be behavioural (inappropriate sleep associations or bedtime resistance), physiological (delayed sleep phase syndrome) or related to underlying mood disorders (anxiety, depression and bipolar disorder). All forms of insomnia are more common in children with learning difficulties, autism, ADHD and sensory impairments (particularly visual). Although behavioural interventions should be the primary intervention and have a robust evidence base, exogenous melatonin is now the first-line medication prescribed for childhood insomnia (Figure 5.3).1 Melatonin is a hormone that is produced by the pineal gland in a circadian manner. The evening rise in melatonin, enabled by darkness, precedes the onset of natural sleep by about 2 hours.2 Melatonin is involved in the induction of sleep and in synchronisation of the circadian system. There is a wide variety of unlicensed fast-release, slow-release and liquid preparations of melatonin. Many products rely on food grade rather than pharmaceutical grade melatonin and some are expensive. In 2018 the European Medicines Agency and UK MHRA approved Slenyto, a paediatric-appropriate prolonged--release melatonin minitablet, for children with autism and insomnia. This approval was on the basis of a phase III multicentre randomised placebo-controlled study of children with autism. Results of the study included clinically significant improvement in caregivers' diary-reported sleep latency, total sleep time and longest sleep period.3 Effects were maintained in the long term. The medication was well tolerated and no unexpected safety issues were reported. The study was the only 'class 1' rated study in the 2020 America Academy of Neurology practice guideline on the treatment for insomnia and disrupted sleep behaviour in children and adolescents with ASD.4 Secondary outcomes showed improvements in children's social functioning and behaviour, and caregivers' well-being. A meta-analysis of melatonin in ASD came to similar, positive conclusions.5 Two RCTs6,7 showed melatonin had comparable benefits when used to treat children with ADHD and insomnia. On this basis, the MHRA in the UK has approved various immediate-release (tablet, e.g. Adaflex) and liquid (e.g. Colonis, Ceyesto) melatonin preparations for the management of sleep-onset insomnia in children with ADHD. There is less evidence (and clinical consensus) for the use of melatonin in typically developing children, although a 2023 meta-analysis provided a conditional recommendation 'for use of melatonin in children and adolescents 2–20 years, who despite optimisation of sleep hygiene practices, continue to present with difficulties in daily functioning, due to chronic insomnia attributed to an underlying disorder'.8 Efficacy A meta--analysis that included adult and paediatric studies of melatonin in primary sleep disorders demonstrated that melatonin modestly decreases sleep-onset latency, increases total sleep time and improves overall sleep quality; effects that appear not to dissipate with continued melatonin use.9 A more recent (2022) analysis confirmed benefits only for sleep latency and sleep duration.10

# 50 - Adverse effects

## Adverse effects

# 51 - Dose

# Dose

Prescribing in children and adolescents CHAPTER 5 Adverse effects Many of the children who have received melatonin in RCTs and published case series had developmental problems and/or sensory deficits. The scope for detecting subtle adverse effects in this population is limited. Screening for adverse effects was not routine in all studies. In early published accounts, melatonin was reported to worsen seizures11 and exacerbate asthma.12,13 Other reported adverse effects included headache, depression, restlessness, confusion, nausea, tachycardia and pruritis.14,15 However, in more recent and larger placebo-controlled studies involving children with learning difficulty, autism and epilepsy,3,16–18 there were no excess adverse effects in the treatment group over placebo and, in particular, seizures were not worsened. A Cochrane review also found no worsening of seizure frequency in patients with epilepsy who were given melatonin.19 Melatonin has no detectable impact on puberty.20 Dose The cut-off point between physiological and pharmacological doses in children is less than 500mcg. Physiological doses (i.e. <500mcg) of melatonin may result in very high receptor occupancy. The doses used in RCTs and published case series vary hugely with between 500mcg and 5mg doses usually being used, although much lower and higher doses have been studied. In one large RCT, 18% of children seemed to respond to a 500mcg dose but others seemed to require much higher doses (12mg).18 Increasing doses above 5mg is likely to provoke the direct sedative effects of melatonin rather than its sleep phase-shifting properties. This might be necessary and helpful for some children with severe and bilateral brain injury. No response to 6–10mg Response Sleep hygiene Parent-led sleep behavioural interventions Melatonin: Use licensed product 2–5mg Consider use of 6–10mg if response poor Discontinue melatonin Identify and treat secondary causes Not effective Childhood insomnia in association with ASD or ADHD Continue at minimum effective dose Figure 5.3 Summary of recommendations in the treatment of insomnia.

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# 53 - Rapid tranquillisation (RT) in children and a

# Rapid tranquillisation (RT) in children and adolescents

Prescribing in children and adolescents CHAPTER 5 Rapid tranquillisation (RT) in children and adolescents As in adults, a comprehensive assessment and effective treatment plan undertaken by staff skilled in the use of de-escalation techniques and appropriate placement of the patient are key to minimising the need for enforced parenteral medication. The differential diagnoses for agitated or challenging behaviour can be broad, but there is concern that RT may be disproportionately used in a neurodiverse population where other strategies may be more appropriate and the outcome more predictable.1,2 Healthcare professionals undertaking RT and/or restraint in children and adolescents should be trained and competent in undertaking these procedures in this population and should be clear about the legal context for any restrictive practices they employ. Be particularly cautious when considering high-potency antipsychotic medication (e.g. haloperidol) especially for those who are neuroleptic naïve, because of the increased risk of acute dystonic reactions in this age group.3 Children are particularly prone to acute extrapyramidal effects of psychotropic and physical medication.4 In the UK, NICE recommends using intramuscular lorazepam (and recommends no other drug).5 Evidence suggests that lorazepam is effective (at a median dose of 1mg) and rarely causes respiratory depression resulting in oxygen desaturation.1 Reviews support the use of a range of SGA drugs6 with the most frequently used agent being olanzapine, which has evidence of its safety and efficacy.7 A wide dose range is given here for medication used in RT. This is partly a consequence of the wide range of body mass in individuals aged from under 10 to 18 years. Caution is required, especially for younger children, but in older adolescents consider the use of adult doses, especially in those who are not drug naïve and where doses at the lower end of the quoted dose range have proved ineffective. A summary is given in Table 5.11. Table 5.11 Recommended drugs for rapid tranquillisation if the oral route is refused or has proven ineffective. Medication Dose Onset of action Comment Olanzapine IM8,9 2.5–10mg 15–30 minutes Possibly increased risk of respiratory depression when administered with benzodiazepines, particularly if alcohol has been consumed. Separate administration by at least 1 hour. Haloperidol IM10 0.025–0.075mg/kg/dose (max. 2.5mg) IM  Adolescents >12 years can receive the adult dose (2.5–5mg) 20–30 minutes Must have parenteral anticholinergics present in case of laryngeal spasm or other dystonia (young people more vulnerable to severe dystonia).  Adult data suggest co-administration of promethazine may

reduce EPS risk.11  ECG is essential Lorazepam* IM12 <12 years: 0.5–1mg;

> 12 years: 0.5-2mg 20–40 minutes Slower onset of action than midazolam  Only treatment recommended by NICE  Flumazenil is the reversing agent for all benzodiazepines. (Continued )

624 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 5 Oral medication should always be offered (and repeated if necessary if the young person is willing to take it) before resorting to parenteral treatment. Oral alternatives such as buccal midazolam14 and inhaled loxapine20 have not been widely investigated in children in RT and have limited availability. Buccal midazolam is commonly used for seizures in children. Monitoring after RT is the same as in adults (see Chapter 3). Medication Dose Onset of action Comment Midazolam* IM, IV or buccal12 0.1–-0.15mg/kg IM  Buccal midazolam 300–500mcg/kg or  6–10 years = 7.5mg;

> 10 years = 10mg 10–20 min IM (1–3 min IV) Quicker onset and shorter duration of action than lorazepam or diazepam  IV administration should only be used (usually as a last resort) with extreme caution and where resuscitation facilities are available.  Quicker onset and shorter duration of action than haloperidol When given as buccal liquid, onset of action is 15–30 minutes.13 There are some published data of its use in mental health but only in adults;14 buccal liquid is unlicensed for this use. Diazepam* IV (not for IM administration)15 0.1mg/kg/dose by slow IV injection  Max. 40mg total daily dose <12 years and 60mg >12 years 1–3 minutes Long half-life that does not correlate with length of sedation  Possibility of accumulation  Never give as IM injection. Ziprasidone IM16,17 10–20mg 15–30 minutes IM Apparently effective  QT prolongation is of concern in this patient group.  ECG is essential. Aripiprazole IM18,19 9.75mg - 15–30 minutes Evidence of effectiveness in adults but no clinical trial data for children and adolescents Promethazine IM <12 years: 5–25mg (max. 50mg/day)  12 years: 25–50mg (max. 100mg/day) Up to 60 minutes An effective sedative, although has a slow onset of action. Useful if the cause of behavioural disturbance is unknown and there is concern about the use of antipsychotic medication in a child or young person. *Note that young people are particularly vulnerable to disinhibitory reactions with benzodiazepines. EPS, extrapyramidal symptoms. Table 5.11 (Continued)

# 54 - References

# References

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# Doses of commonly used psychotropic drugs in children and adolescents

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626 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 5 Doses of commonly used psychotropic drugs in children and adolescents Commonly used psychotropic drugs are presented in Table 5.12. References


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2. Merative US LP. Micromedex. 2024; https://www.micromedexsolutions.com/home/dispatch/.
3. Gov.UK. Guidance: Valproate use by women and girls. 2018 (last updated January 2024); https://www.gov.uk/guidance/valproate-use-by- women-and-girls. Table 5.12 Starting doses of commonly used psychotropic drugs in children and adolescents.1,2 Drug Starting dose* Comment Antipsychotics Aripiprazole 2mg Adjust dose according to response and adverse effects. Clozapine 6.25–12.5mg Use plasma levels to determine maintenance dose. Lurasidone 18.5mg (20mg) to 37mg (40mg) Adjust dose according to response and adverse effects. Olanzapine 2.5–5mg Adjust dose according to response and adverse effects. Quetiapine 25mg Effective dose usually in the range 150–200mg daily. Risperidone 0.25–2mg Adjust dose according to response and adverse effects. Antidepressants Citalopram 10mg daily Effective dose 10–40mg (note QT effects) Escitalopram 5mg/day Effective dose 10–20mg (note QT effects) Fluoxetine 5–10mg/day Adjust dose according to response and adverse effects. Sertraline 25mg daily Effective dose usually in the range 50–100mg daily. Other drugs Lithium 100–200mg/day lithium carbonate Use plasma levels to determine maintenance dose. Melatonin 1–2mg at night Effective dose 2–10mg Valproate 10–20mg/kg/day in divided doses Use plasma levels to determine maintenance dose. Do not offer valproate to girls or young women of child--bearing potential unless there is a pregnancy prevention programme (PPP) in place.1,3 *Suggested approximate oral starting doses (see primary literature for doses in individual indications). Lower dose in suggested range is for children weighing less than 25kg.