Pharmacological Approaches in Child and Adolescent Mental Health

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Abstract

While psychological therapies remain the first-line treatment for most child and adolescent mental health disorders, there is increasing evidence to support the use of medications especially where a psychological treatment has been ineffective. When using psychotropic medications in children and adolescents, it is particularly

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important to maintain good prescribing practice. This chapter highlights several key principles of prescribing including the importance of properly defining the patient's problem and specifying the therapeutic objectives, working with a selection of preferred drugs that you are very confident with, giving good and clear information about potential benefits and risks, and closely monitoring outcomes. In addition to these general principles, there is also a discussion on polypharmacy and drug x drug interactions, the importance of changing things one step at a time, adherence to treatment, and initiation of treatments. Therapeutic options and strategies are discussed for the most common mental health disorders of childhood and adolescence covering attention deficit hyperactivity disorder, depression, anxiety, obsessive–compulsive disorder, autism spectrum disorder, tics and Tourette's, bipolar disorder, and schizophrenia. Advice is given about approaches to measurement-based care and structured approaches to adverse effects.

Keywords

Psychopharmacology · Pediatric · Good prescribing practice · Mental health · Psychiatry · ADHD · Depression · Anxiety

Introduction

For most child and adolescent mental health problems, psychological therapies are, rightly, considered to be the first-line treatment option. This approach, to try a non-pharmacological approach first, is supported by a considerable and growing evidence base and is recommended by many evidence-based guidelines for a broad range of disorders ranging from depression, anxiety, obsessive–compulsive disorder (OCD) and post-traumatic stress disorder (PTSD), eating disorders, substance use disorders and attachment disorder to oppositional defiant disorder (ODD), conduct disorder (CD), Tourette's and the irritability and aggression associated with autism spectrum disorders (ASD), or intellectual disability (ID). There are however several disorders such as attention deficit hyperactivity disorder (ADHD), bipolar disorder, and schizophrenia where it is now agreed that a pharmacological approach can legitimately be considered as a first-line treatment approach. While it is not surprising that the use of medication to treat psychiatric problems is far less common in children and adolescents than in adults, it is also clear that the rates of prescription of psychotropic medication are increasing in these younger age groups. Despite a significant increase in the number and quality of the clinical trials of psychotropic medications in children and adolescents, there are legitimate concerns that the increase in rates of prescribing still outstrips the evidence base. One example from the UK concerns the prescribing of antipsychotics for children 7–12 years of age in primary care which almost tripled between 1992 and 2005, with the prescribing of atypical antipsychotics increasing 60-fold from 1994 to 2005 (Rani et al. 2008). The vast majority of this increased prescribing was for the management of aggression and challenging behaviors rather than for psychosis. It is not clear whether this increase

in prescribing of antipsychotics to children should be viewed as an indication of appropriate clinical practice in the management of often very complex and debilitating conditions or raising concerns about safety of prescribing potent medications that may be a consequence of poor understanding about the non-pharmacological options available to treat these behaviors or a genuine lack of access to non-pharmacological treatments. The truth is likely to be a combination of the two but does highlight the need for better evidence to allow this kind of clinical decision-making more evidence-based.

Against this backdrop of increased prescribing, it is clearly important for all professionals working with child and adolescent mental health problems to have a good understanding of the appropriate use of psychotropic medications including both their potential benefits and adverse effects in these populations. For those readers with a strong grounding in adult mental health, it is reassuring to know that many of the issues around prescribing psychotropic medications in children and adolescents are similar to those in adults. However, there are also several important differences that need to be taken into account.

General Issues

Although medications are not considered to be the first-line treatment for most child and adolescent mental health disorders, they can make an important contribution to the overall management, particularly where a psychological therapy has either failed or only partially improved the clinical presentation. It is important that medical and nonmedical clinicians working in child and adolescent mental health services or within a pediatric setting don't fall into the familiar trap of adopting a polarized view about medication and psychological approaches to treatment. They can complement each other well if used thoughtfully and knowledgeably.

In children and adolescents with psychiatric disorders, medication is nearly always deployed alongside psychosocial interventions and integrated into a total treatment package which should also include a strong psychoeducational component; it is, or at least should be, uncommon for medication to be the only form of intervention. One particular benefit of medication, often undervalued by clinicians, is the ability to put a child or adolescent in a position whereby they are more able to take full advantage of a psychotherapeutic intervention. On the other hand, there are clear indications that psychotropic medications are being increasingly used in children and adolescents, and while evidence is sparse, there is a growing concern that in some instances medications are being used either to compensate a lack of availability of, and access to, adequate high-quality psychosocial treatment or as a "quick fix" for problems that would more appropriately be managed through a psychological intervention.

Most of the conditions for which medication is useful affect older children and adolescents (see Table 1), and it is unusual to prescribe psychotropic medications for preschool children. The reactions of very young children to psychotropic medication are much less predictable and are associated with increased rates of adverse effects compared to older children and adolescents who are themselves more susceptible to

Table 1 Summary of the main medications used in child and adolescent mental health disorders

Class	Main drugs within class used in children and adolescents	Main indications
Stimulants	Methylphenidate Amphetamines Lisdexamfetamine	ADHD Binge eating disorder
Non-stimulant ADHD medications	Atomoxetine	ADHD
Alpha 2 agonists	Guanfacine Clonidine	ADHD Tics and Tourette's Sleep disorders
Serotonin reuptake inhibitors Selective	Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline	Depression Anxiety OCD
Less selective	Clomipramine	
Other antidepressants	Bupropion Venlafaxine	ADHD Treatment-resistant depression
Atypical antipsychotics	Risperidone Aripiprazole Quetiapine Olanzapine Lurasidone Brexpiprazole	Schizophrenia Mania Tourette's Irritability, aggression (in ASD and ID)
Mood stabilizers	Carbamazepine Valproate Lithium Lamotrigine Gabapentin Topiramate	Mania, bipolar disorder Irritability, mood instability, aggression
Other drugs	Melatonin	Sleep disorders

adverse effects than adults. It is also important to note that some psychotropic medications (e.g., fluoxetine) have been demonstrated, in animal studies, to lead to lasting developmental changes to the immature brain although the implications of this for humans remain unclear. For these reasons, it is strongly suggested that clinicians approach the use of any of the medications mentioned in this chapter in the very young child ($\leq$5 years) with great caution and continue to exert a degree of caution for those medications not adequately trialed in children and young people while their brains are still developing (which we now understand extends well into young adulthood – late 20s).

It is also important to always consider for whose benefit a medication is being prescribed. It is, for example, becoming more common for the parents or teachers of children with disruptive behaviors to ask for, and sometimes "insist" on, medications to make their child easier to manage. If this results in improved family relationships,

a more settled household and a happier child then perhaps can be justified, but enabling an easier life for adult caregivers or educators is an insufficient reason to prescribe, particularly when balanced against the very real risk of long-term metabolic and motoric adverse effects.

Good Prescribing Practice for Child and Adolescent Mental Health Problems

Whenever we consider prescribing a medication for a mental health problem, it is highly recommended to run through a checklist of questions and practice points to make sure that the decision to prescribe is justified, that the best medication is chosen at the correct dose, that the target symptoms are clear and appropriate, that outcomes can be measured and monitored, and that the patient, and where appropriate their family, are fully informed of potential risks as well as benefits of the treatment choices and are in agreement with the treatment plan. While it is easy to skimp on these preparatory steps, failing to follow them is likely to have a negative effect on outcomes.

There are several very-well-thought-through approaches to ensuring good prescribing practice which, with a few tweaks, can be easily applied to child and adolescent psychopharmacology. Coombes and colleagues (2011) highlight the four important stages of prescribing:

1. *Information gathering*: This requires the prescriber having the requisite skills to gather the relevant patient information including current symptoms and diagnosis, medical and psychiatric history, current and past medication history, and allergies and adverse drug reactions.
2. *Clinical decision-making and treatment planning*: Using pharmacological knowledge along with details of the diagnosis and clinical presentation as well as demographic and developmental information to select the most appropriate medication and the most appropriate dosing protocol for that individual patient. At this stage, it is essential to consider non-drug treatments, and give the patient and their family enough information to engage them in collaborative decision-making as this has the potential greatly to improve adherence and patient outcomes. The prescriber should be able to tailor their decision-making styles, to be more or less directive or collaborative, and decide which is most appropriate for the patient at that point in time, while always considering and valuing the patient's/carers' views.
3. *Communication:* The prescriber needs to then be able to communicate their prescribing decisions in a clear, safe, and effective manner to the patient and any other health professionals that are involved in the case. Prescriptions should always be legible, unambiguous, and without error-prone abbreviations safe dispensing. The management plan should also be clear and contain triggers for review should any serious and/or unexpected adverse events emerge. Monitoring

requirements, potential adverse effects, and contingency planning should also be discussed.

4. *Monitoring and review:* The prescriber should be available to review the therapeutic and/or adverse effects of the treatment to inform dose adjustments or a change in treatment. As discussed below, measurement-based care, the process by which changes in treatment are based on regular operationalized and structured outcome measures, is not yet common in psychiatric practice. There is however strong evidence that this approach delivers improved outcomes. Hopefully, these approaches will soon be recognized as standard practice.

The World Health Organization has also proposed several key steps that can be followed to improve good prescribing practice, and their manual, "Guide to Good Prescribing: A practical manual," would make a welcome addition to every prescribers bookshelf, computer, or device (De Vries et al. 1994). They propose six key steps that overlap neatly with the four-stage process described above: (1) define the patient's problem; (2) specify the therapeutic objective; (3) verify the suitability of your P-drug; (4) write a prescription; (5) give information, instructions, and warnings and; (6) monitor (and stop?) the treatment. They also highlight the importance of staying up to date about new drug developments and information. One interesting and important contribution of this manual is the introduction of the need for clinicians to select their P(ersonal) drugs. P-drugs are the drugs that a clinician has access to and has chosen to prescribe regularly and with which they have become familiar. They are a prescriber's priority choice for any given indication and situation. The P-drug concept includes much more than just the name of the drug; it also includes the formulation, dosage, and titration schedule and duration of treatment. P-drugs will differ from country to country, and between individual doctors, depending on availability and cost as well as medical culture and individual interpretation of information (although with the acceptance of evidence-based practice, there should be less variation in the last two). The principle is however a universal one: choose your preferred drugs based on availability, cost, and evidence and use them where appropriate. This avoids repeated searches for a good drug in daily practice and allows the prescriber to become thoroughly familiar with their effect profile of positive and negative (adverse effects). This familiarity has clear benefits to the patient. The WHO manual has some very good tips for how and how not to select our list of P-drugs (De Vries et al. 1994).

Other factors to take into account when prescribing psychotropic medications for children and adolescents include:

1. The well-known mantra of "start low go slow," although it is also important not to start too low or go too slow as this increases the risk of undertreatment and of the patient dropping out due to a too slow response time. Titration is therefore an important balancing act between achieving optimal response with the least adverse effects. This is another strong argument for having a portfolio of P-drugs that you know well and can be confident about prescribing.

2. Address issues that may impact on adherence at the very beginning. Young people are not alone in their ambivalence about taking medication on a regular basis, but for many adolescents, it is an even more unwelcome imposition. This is particularly true if a decision to start a medication is made simply on the basis of a discussion with parents. Adherence can be improved if the clinician takes time to have an individual discussion with the child/young person about why the medication is being prescribed, what the benefits may be, what adverse effects can be expected, how long before any positive effects will be seen, and how long it is anticipated the course will be. These discussions form the necessary basis for informed consent and are good practice even with children too young to be competent to grant or withhold consent. Most people only remember a small proportion of what has been said in the clinic, so the use of developmentally appropriate handouts describing the drug in question is often helpful and much more likely to be of use than the data sheets supplied by the manufacturers.
3. Only change one thing at a time. When making changes in dose or switching between drugs in order to either improve effectiveness or reduce adverse effects, it is important to make only one change at a time. It is very tempting not to follow this rule when things are not going well and you have several ideas for how to improve them. However, if you make more than one change at a time and things either improve or get worse, it is often extremely difficult to know which of the changes made the difference. This may or may not be a problem at the time (depending on whether the changes went well or not) but will always make it difficult in the future if and when further adjustments are required.
4. Avoid polypharmacy wherever possible. While it is sometimes necessary to prescribe more than one medication at a time (e.g., when treating ADHD and bipolar disorder at the same time), polypharmacy should not be the norm for most child and adolescents. From clinical observation, one of the major issues seems to be that a failure to up-titrate patients to the optimal dose results in an additional medication being added to manage a partial response to the first medication. This can result on patients being treated with multiple drugs for essentially the same problems. It is always preferable to titrate the first drug up to maximum dose or maximum tolerated dose (as long as this is within safe limits) rather than to add a second medication. Also where there is a suboptimal response to a first medication, consider switching to another medication rather than adding a second to the first. Some helpful questions to ask before switching or adding are provided in Box 1.
5. Always pay attention to possible drug x drug interactions. Many psychotropic medications are metabolized by the CYP family of hepatic enzymes and most importantly the CYP450 isoenzymes. As a consequence, there are many drug x drug interactions whereby the metabolism of one drug is altered by another. This can lead to both inhibition and induction of the CYP enzymes which results in either decreased or increased drug metabolism. When prescribing two drugs at one time, it is therefore important to check for these, and other, potential drug x drug interactions. There are now several helpful online references that can be checked for current information on medications and drug interactions. The British

National Formulary (BNF) which can be accessed through MedicinesComplete (https://www.medicinescomplete.com/#/) is particularly helpful in child and adolescent health as it includes access to the BNF for Children.

6. Think like a chess player and try to work out whether the change you make now has the potential to hinder you in the future. An example of this from ADHD practice is when titrating onto a psychostimulant. You have increased the dose and symptoms have improved considerably and there are no adverse effects. Should you leave the dose as it is or increase further? My personal practice would be to increase the dose to ensure I have optimized treatment to maximum benefit. There are several advantages to this approach. If there is a further improvement, the benefits are clear. If there are not or there are adverse effects at the highest dose, it is easy to say "Ok we now know the best dose for you" and drop the dose back down. But another potential longer-term benefit is that if the patient comes back in 6 months and reports that their medication is now not working as well, we would be clear that this is likely to be due to tolerance rather than suboptimal dosing. In this case, the treatment approach would be to stop the medication for a brief (perhaps 1 week) period and then restart it, and it is likely to work better again. If we did not know this from our early experience with titrating to optimal effect, we may be tempted to just increase the dose. This would of course provide a temporary solution to the tolerance, but after a short period, it would reoccur and we could get into a spiral of increased dose to counteract tolerance.
7. Make sure the patient will be able to take the medication being offered. Not all children find swallowing tablets and capsules easy, and liquid preparations of medicines are often not available. It may be necessary to teach a child how to swallow a tablet using a graded series of small cake decorations and sweets, ensuring that swallowing a solid item is always followed by a drink.
8. Keep medications safe. Parents need to be reminded to keep medications safe and secure and should supervise the taking of them. This is particularly important with controlled drugs such as the stimulants.
9. Always prescribe within the limitations of your knowledge, skills, and experience. This may seem obvious but we often end up in situations we are not familiar with. In times like this, it is always appropriate to stop, take a step back, and ask for advice from a colleague or consult the literature. Common examples of such situations are when switching from one drug to another with questions like: Should I stop one drug before starting the other or should I cross taper between drugs? How slowly should I reduce the dose, or how quickly should I increase the dose? Are there any drug x drug interactions I should be aware of and if so how do I manage them?

Off-Label Prescribing

Although the number of psychotropic medications "licensed" for use in children and adolescents with mental health problems is increasing, it is still the case that for most disorders most medications in most countries are not "licensed" and need to be used

"off-label." A drug license is a "marketing authorization" meaning that a pharmaceutical company has been granted permission to promote a drug for a specified indication by a national or international regulatory body. Off-label prescribing occurs when medication use falls outside the scope of the marketing authorization with respect to one or more of four key domains (the "4 Ds"): (1) the disorder being treated, (2) the demographics (primarily age) of the patient, (3) the dosage being prescribed and route of administration, and (4) the duration of treatment (Baldwin and Kosky 2007). While prescribing a medicine in a circumstance that is specified as contraindicated would also constitute off-label use, this is not the same as using one outside the "4 Ds," which is often very appropriate. Until recently, it was relatively uncommon, apart from ADHD medications, for companies to test new drugs on children, and there was neither a requirement nor incentive for them to do this. More recently, the Food and Drug Administration (FDA) in the USA and the European Medicines Agency (EMA) in Europe established a system of obligations, rewards, and incentives to ensure that new medicines are properly researched, developed, and authorized to meet the therapeutic needs of children. This has ensured that companies will consider the potential pediatric use of medications they develop and conduct specific programs of research where there is potential for their use in children and adolescents. This has increased the number of clinical trials for psychotropic medications and over time will result in a stronger evidence base not only for efficacy of medications in this population but also specific data on safety and tolerability.

Unfortunately, these regulations do not apply to existing drugs, and it will therefore still be necessary to prescribe most of the medications we are familiar with, and that are more widely available across the globe, off-label.

When prescribing off-label, it is helpful to consider several factors in addition to those discussed above. The British Association of Psychopharmacology recently published a checklist of helpful recommendations to guide clinical practice in this area (Sharma et al. 2016).

1. Be familiar with the evidence base for the psychotropic agent, including its pharmacokinetic profile in children, the potential for adverse effects, any drug–drug interactions, and differences in bioavailability/stability of the intended formulation.
2. Prescribing an off-label medicine may have advantages over a licensed one. Hence, licensed drugs and formulations should not always be prescribed and supplied in preference to an off-label drug or formulation. A prescribing decision (including a decision not to prescribe) should incorporate knowledge of the overall evidence base and the needs of the individual child.
3. When the evidence base for an off-label medication is lacking or the benefit/risk profile appears potentially unfavorable, obtain a second opinion from another doctor (and perhaps another member of the multidisciplinary team) before prescribing.
4. Explain the potential benefits and side effects to the patient and their parents/carers and document this discussion in the medical record.

5. Provide information leaflets for off-label medications specifying use in children and adolescents, including indications, dosage, and route of administration.
6. "Start low and go slow" and actively monitor response using standardized instruments and whether there are any adverse effects.

Dosing and Variation in Pharmacokinetics in Children and Adolescents

Another important consideration when prescribing for children and adolescents is dosing. Although there are certainly circumstances when children and adolescents will require lower doses than adults with the same condition, this is not always the case and sometimes prescribers are overcautious and give too low a dose. In general pediatric practice, doses are most often calculated according to body weight or surface area. Although this can be useful in determining the starting dose of a psychotropic medication in a prepubertal child, for most psychotropic medications, the weight/dose relationship is not closely correlated. It is therefore more effective to titrate according to response and adverse effects rather than by weight or surface area. Drug response does however generally vary with age, weight, sex, and disease state as these factors can impact on pharmacokinetics (absorption, distribution, metabolism, and excretion). While it would appear that young people often need adult doses of psychotropic medications in their early teens, dose finding studies have never been adequately conducted for many of the older more established medications. Interestingly, children and young people may in fact metabolize medications more efficiently than adults. For example, for the stimulants used in ADHD, where there is a strong association between pharmacokinetics and pharmacodynamics (Sonuga-Barke et al. 2004), the level and frequency of dosing may need to be greater for children and adolescents than that for adults. Individual variation in dose response is most strongly related to the variation in metabolism of medications which often reflects differences in the efficiency of hepatic enzymes. Hepatic metabolism develops gradually in the first year of life but then peaks in early childhood and by middle childhood (6–12 years) is twice that of adults. It then plateaus down to adult values in the early teens. Thus, for drugs with a primary hepatic metabolism (e.g., most antidepressants, amphetamines, atomoxetine), many children **may require higher mg/kg doses** than adults. There are also inter-individual differences in rate of development of renal function: it develops much earlier and closely resembles that of adults by the end of the first year.

Therapeutic drug monitoring refers to the measurement of drug levels in body fluids (predominantly blood) and the use of these levels to adjust dose. In child and adolescent psychopharmacology, therapeutic ranges have been suggested for lithium, imipramine, and nortriptyline and the anticonvulsants valproate and carbamazepine which are used as mood stabilizers (Rosen 2017; Ryan 1990; Rylance and Moreland 1980). It is however hardly ever used and is not generally recommended for other psychotropic medications.

Medication Treatments for Specific Disorders

Although the rest of this book is not organized by diagnostic categories for this chapter, we will adopt a disorder-/problem-based approach. This was chosen over a drug-based approach for two main reasons. For many disorders, drugs from different classes will be considered. As it is the patient with a particular problem that we are treating, it makes more sense to look at the different therapeutic options for each disorder/problem rather than listing the different disorders under each drug class. Also clinical trials tend to be focused on a particular disorder/presentation meaning that the evidence base is organized by disorder rather than by drug. One important reason for this is that, when considering whether to license a medication, all of the major regulators ask that this is done with respect to a particular disorder.

Medication Treatments for ADHD

There has been more research into the use of medication for the treatment of ADHD than any other area of child and adolescent psychopharmacology, and most clinicians are now comfortable with the idea of using medications as a part of their treatment of ADHD. While for some considerable time it has been agreed that stimulant medications (methylphenidate and amphetamine derivatives) should be the first-line treatment for severe ADHD, opinions have been divided about whether medication or parent training approaches should be considered as the first treatment option for those with mild-to-moderate ADHD. While those in the USA have always leant toward medication as a first treatment for all cases of ADHD, those in Europe have, until recently, been more cautious. However, following publication of a series of systematic reviews and meta-analyses that found that while parent training improved parenting and conduct disorder outcomes, it had very little, if any, impact on core ADHD symptoms (Daley et al. 2018; Sonuga-Barke et al. 2013), attitudes have shifted, and the most recent NICE guidelines support the use of medication as a first-line treatment for children and adolescents in the UK aged 6 years and over (Nice 2018). Other guidelines (e.g., those recently published in Germany) still recommend parent training as a first-line treatment for those with mild ADHD.

Several medications are licensed for the treatment of ADHD in countries around the globe. However, there is considerable variation between different countries with respect to which medications are licensed and reimbursed; and even where a medication is available, there is considerable variability with respect to which particular preparations are available. ADHD medications can be broadly separated into stimulant and non-stimulant medications.

Stimulant Medications

There are two main classes of stimulant used to treat ADHD: methylphenidate- and amphetamine-based medications which include dexamphetamine, mixed amphetamine salts, and the dexamphetamine prodrug lisdexamfetamine. Immediate release and extended prelease preparations of methylphenidate and the amphetamines are

available in some countries. The extended-release preparations differ in terms of the proportion of immediate-release to extended-release methylphenidate and with respect to the intended duration of action. Typically, immediate-release preparations have expected durations of action of between 4 and 6 h and require multiple dosing across the day (usually two or three times a day). The extended-release preparations have proposed durations of action of either 8 or 12/13 h and vary considerably in the balance between immediate- and extended-release proportions. Importantly, these differences do not mean that one preparation is better than the other. They do, however, help to understand the important differences between the various preparations and the different ways they will be dosed. It is essential that clinicians become familiar with the preparations available in their counties and understand not only the duration of action but also the immediate-release component of the various doses. A failure to do so is one of the most common reasons for treatment failure following a switch from one preparation to another within the same class. A chart describing the different preparations of methylphenidate available in the UK is provided in Coghill and Sinita (2014), and a detailed discussion of the extended-release preparations can be found in Banaschewski et al. (2006). Lisdexamfetamine which was developed after the publication of these articles is a dexamphetamine prodrug that has an extended duration of action, up to 13 h. The extended duration of action for lisdexamfetamine is a function of the metabolic processes that cleave the dexamphetamine molecule from the lysine and the impact of this on the metabolism of the released dexamphetamine rather than being due to a mechanical delivery mechanism.

Non-stimulant Medications

The non-stimulant medications licensed for use in ADHD are atomoxetine and extended-release preparations of guanfacine and clonidine (clonidine US only).

Atomoxetine is a specific noradrenaline reuptake inhibitor that is effective and safe in treating ADHD and has a low abuse potential. Atomoxetine is generally not as immediately effective as the stimulant medications but can be effective in cases that either do not respond or are unable to take or tolerate stimulants. Although some patients get very clear benefits at around 4 weeks, there are some for whom it may take up to 12 weeks for clinically relevant effects to be seen, and this is worth discussing with patients when they commence treatment.

An extended-release preparation of the alpha 2 agonist guanfacine has been licensed for the treatment of ADHD in several countries around the world, and extended-release clonidine is available in the USA. While both drugs have been demonstrated to be efficacious as stand-alone treatments for ADHD, which like atomoxetine makes them useful for stimulant non-responders, it is perhaps their potential as adjunctive treatments, co-prescribed alongside the stimulant preparations (Dittmann et al. 2018), that is most clinically relevant. Clinical trial data supports the co-administration of guanfacine and methylphenidate both from a safety and efficacy perspective. This is important as the potential for increased adverse effects, particularly blood pressure, pulse, and other cardiac signs and symptoms, needs to be considered before co-prescribing atomoxetine with a stimulant (something the author is very reluctant to do on the grounds of safety).

When choosing which medication to start with when treating ADHD, the first consideration is of course availability. Assuming availability of both methylphenidate and one of the amphetamine medications, the advice until recently was that they are both equally good and that there was no clear benefit of one over the other. Indeed, both methylphenidate and the amphetamines work well for about 70% of those with ADHD, and between 90% and 95% of patients will respond well to one, the other, or both. The most sensible approach is therefore to start with one, and if the patient does not respond and there are no contraindications, switch to the other. Importantly, just as some people do not show a clinical response to one class of medication (i.e., methylphenidate or amphetamine) but do to the other, not everyone who has adverse effects to one will also get them to the other. More recently, the results of a network meta-analysis have suggested that for children and adolescents, methylphenidate may have some slight benefits over the amphetamines (including lisdexamfetamine), while amphetamines (and lisdexamfetamine) are slightly superior in adults. For those who have a partial response to one of the stimulant medications, it is worthwhile considering co-administration of extended-release guanfacine (or ER clonidine where available). Immediate-release clonidine and guanfacine may be beneficial to some patients where the ER versions are not available; but they have much shorter half-lives and need to be given several times across the day. They may be more likely to result in hypotension when taken and a rebound hypertension if stopped abruptly. For those who do not respond to a stimulant, then atomoxetine and the alpha 2 agonists may be effective as monotherapies and should be considered.

There are still some countries where access to stimulant medications is prohibited by law. In these countries, atomoxetine (or extended-release guanfacine if available) would be considered as the first-line treatment option. When prescribing atomoxetine in these circumstances, it is essential to make sure that the patient has a long enough trial of medication to allow for response. We would suggest at least 12 weeks at a dose of 1.2 mg/kg/day (up to a maximum of 100 mg). The alpha 2 agonists clonidine and guanfacine may be considered if atomoxetine is unavailable or ineffective. The extended-release preparations are preferred as they will have a more stable effect across the day and a lower risk of hypotension and rebound hypertension. If the immediate-release versions are prescribed, they need to be given in multiple doses to ensure coverage across the day. Other non-stimulant medications that have some, rather limited, evidence of efficacy in ADHD include bupropion, buspirone, tricyclic antidepressants (although these, desipramine in particular, have been demonstrated to be associated with increased cardiovascular adverse effects), metadoxine, and mazindol. Those considering prescribing one of these agents for ADHD should consult the specialist literature which has been well-reviewed by Dittmann and colleagues (2018).

Practical Issues in the Pharmacological Management of ADHD

The publication in 1999 of the primary findings from the NIMH Collaborative Multisite Multimodal Treatment Study of Children with Attention Deficit/Hyperactivity Disorder (MTA study) marked a milestone in child and adolescent

psychiatry research. A full discussion of the findings of the MTA study is beyond the scope of this chapter, and readers are referred to the excellent overviews and summaries of the trial itself and the longer-term outcomes of the participants (Swanson et al. 2008a, b, 2018).

One of several very interesting initial findings from the MTA study was the superiority of the MTA medication protocol over the community treatment arm (within which the majority of patients received medication). It seems likely that the treatment algorithm developed for the study, which included highly structured titration and continuing care protocols and which aimed for maximal effect with "no room for improvement," only allowing a dose decrease for moderate to severe side effects, was responsible for these differences. As a consequence, those in the medication arm received higher doses of medication and were usually on medication designed to cover 12 h of the day in contrast to the community group who were usually on 8-h dosing regimes. The MTA medication protocol also had an initial intensive "forced dose titration" to optimal dose, and treatment changes were informed by detailed feedback from both parents and teachers. It has been proposed that it was the withdrawal of this structured support, rather than decreased efficacy of medication over time, that resulted in the less positive outcomes reported for the medication management group at the later follow-up visits (Banaschewski et al. 2009) although this is still being debated (Coghill 2019; Swanson 2019; Banaschewski et al. 2009; Jensen et al. 2007; Molina et al. 2009). While it would be unrealistic to integrate the full protocol into day-to-day clinical practice, they can quite easily be adapted and scaled down while retaining key components such as measurement-based care and a clear structured approach to dose optimization through titration. Adopting this approach, Coghill and Seth (2015) were able to significantly improve care in a publicly funded clinical service in the UK. This emphasizes the important benefits that can be realized through the implementation of measurement-based care approaches not only in ADHD but more generally in child and adolescent mental health (Liu et al. 2019).

It is equally important to take a structured approach to assessing adverse events associated with ADHD medications. These have been comprehensively reviewed by the European ADHD Guidelines Group (EAGG, Cortese et al. 2013). While the long-term effects of stimulant medications on growth are important, arguably the most important issue is the identification of cardiac risk prior to starting treatment and ongoing management of cardiovascular adverse effects. While it is not necessary to perform an ECG for every patient before starting ADHD medications, it is essential to screen for other, potentially important, cardiac risk factors. The EAGG has suggested that routine questions about personal history of cardiac disease, history of sudden death in a close relative before the age of 40 years, and symptoms of cardiac disease (effort intolerance, frequent palpitations, and frequent syncope – particularly exercise induced) should be asked as well as enquiring about other medications that could cause cardiac problems. Positive findings should prompt the clinician to consider ECG (preferably a 24-h tape or 12 lead if this is not available) and/or a discussion with a cardiologist (Cortese et al. 2013). Although the average increases in pulse and blood pressure with ADHD medications are

modest, there is a proportion of individuals who experience clinically significant increases. The EAGG further suggest that a heart rate consistently above 120 beats per minute should not be accepted without review and that a blood pressure above the 95th centile should be considered abnormal and be followed up.

Medication Treatments for Depression

The use of medication to treat adolescent depression remains contentious. In the UK, the NICE guidelines for depression in children and adolescents are clear that antidepressant medications should not generally be used as an independent initial treatment for depression in children and adolescents (Nice 2017). They suggest that specific psychological therapy (cognitive behavioral therapy or interpersonal psychotherapy) is offered to all patients with moderate to severe depression. In young people (12–18 years), the combination of medication treatment with psychological therapy can be considered for initial treatment of moderate to severe depression instead of psychotherapy on its own. Fluoxetine is currently the only antidepressant recommended as a first-line medication for depression in children and adolescents.

In 2013, Hazell and Mirzaie published an influential Cochrane review (Hazell and Mirzaie 2013) which demonstrated that tricyclic antidepressants are not effective in treating depression in children and adolescents and are associated with several significant adverse events. In the early 2000s, there was a rapid increase in the use of selective serotonin reuptake inhibitors (SSRIs) in children and adolescents. Their initial use significantly out stripped any evidence for efficacy. There are now several RCTs comparing SSRIs with placebo in children and adolescents although these are not all of high quality. There are consistently positive RCTs for fluoxetine and mixed results for sertraline, citalopram, and escitalopram (reviewed comprehensively by Usala et al. (2008)). There are also negative results for trials comparing paroxetine, venlafaxine, nefazodone, and mirtazapine with placebo (all unpublished "data on file"). A comprehensive network meta-analysis of trials within this age group concluded that only fluoxetine was statistically significantly more effective than placebo and that, in terms of tolerability, fluoxetine is also better than duloxetine and imipramine and that imipramine, venlafaxine, and duloxetine are less well tolerated than placebo (Cipriani et al. 2016). From an evidence-based perspective, fluoxetine should clearly be the first-choice antidepressant for adolescent depression. Most SSRIs are metabolized by the cytochrome P450 family of enzymes, and fluoxetine (2D6, 3A4, 2C19), paroxetine (1A2, 2C19), and to a lesser degree fluvoxamine (2D6, 2C9) and sertraline (2D6) are all associated with inhibition of various P450 isoenzymes. Citalopram and escitalopram do not inhibit 2D6 and are therefore less likely to result in drug x drug interactions and may on occasion be preferred for this reason. They were not however either as effective as fluoxetine or better tolerated than other SSRIs in the network meta-analysis of Cipriani and colleagues (2016).

Several high-quality studies have compared treatment with antidepressants. The publicly funded Treatment for Adolescents with Depression Study (TADS) in the USA (March et al. 2004) and the Adolescent Depression Antidepressants and

Psychotherapy Trial (ADAPT) in the UK (Goodyer et al. 2007) have both investigated combination treatment with CBT and an SSRI (in TADS this was fluoxetine; in ADAPT it was most often fluoxetine) compared with the SSRI alone. The TADS study also included groups receiving CBT alone and placebo. In TADS, both combination treatment and fluoxetine alone were more effective than placebo after 12 weeks of treatment, with the combination being the most effective treatment. In TADS, CBT alone was less effective than fluoxetine and no more effective than placebo. In the 28-week ADAPT study, both the SSRI and SSRI + CBT groups improved, but there was no significant difference between the two groups.

Taken together, these data support the conclusions of NICE that the combination of an antidepressant plus a psychological therapy can be considered for initial treatment of moderate to severe depression instead of psychotherapy on its own. Around 60%, however, of young people with depression will respond adequately to initial treatment with an SSRI; so it is important to consider the most appropriate approach to treating non-responders. This was the focus of the National Institute of Mental Health-funded Treatment of Resistant Depression in Adolescents (TORDIA) trial. TORDIA enrolled adolescents whose depression had not responded to an "adequate trial" of an SSRI. Participants were randomized to one of four treatments (switch to another SSRI; switch to venlafaxine; switch to another SSRI + CBT; switch to venlafaxine + CBT) (Brent et al. 2008; Emslie et al. 2010). After the first 12 weeks, just under 50% of participants had now responded to the switch in treatment. The combination of CBT with a switch to another antidepressant resulted in a higher rate of clinical response than a medication switch alone. For those who had a simple switch of medication, a switch to another SSRI was just as effective as a switch to venlafaxine and resulted in fewer adverse effects. At week 12 after randomization, non-responders were offered open treatment (a switch to another antidepressant, augmentation, or the addition of CBT or other psychotherapy) for a further 12 weeks. At 24 weeks, 38.9% of those enrolled in the study had achieved remission with the likelihood of remission much higher (61.6% vs. 18.3%) among those who had already demonstrated clinical response by week 12 (Emslie et al. 2010). All participants were treated naturalistically from week 24 onward; the remission rate rose to 50% by week 48 and to 61% by week 72. However, 72% of participants still had at least one residual symptom of depression, such as irritability or low self-esteem, at week 72, and 11% met diagnostic criteria for major depression. The study authors make a good point in suggesting that clinicians should pay significant attention to those patients who do not respond in the first 6 weeks of treatment and consider either a combination treatment or switching to another SSRI for such cases.

Suicidality

Although several nonpsychiatric factors are associated with increased risk of suicidal ideations and suicidal behavior, suicidality and depression are of course closely linked, and regular assessment of risk for suicide is a key part of management of depression. In children and adolescents, this has been complicated by the suggestion

that there may be an association between treatment with SSRI antidepressants and suicidality. A recent Cochrane meta-analysis showed that for 16–18-year-old patients with a depressive disorder, there was an increased risk of suicidal behaviors and ideations (there were no completed suicides in the included trials) for those on antidepressants compared with those receiving placebo (17 trials; N = 3229; RR 1.58; 95% CI 1.02 to 2.45) (Hetrick et al. 2012). In the TADS study, suicidality decreased substantially in all treatment groups with improvement in suicidality greatest for the combined treatment and least for fluoxetine alone. Importantly however fluoxetine did not increase suicidal ideation. The authors concluded that suicide-related adverse events are uncommon but may occur more often in patients treated with fluoxetine than in those treated with combined treatment or CBT alone and that CBT may protect against suicide-related adverse events in fluoxetine-treated patients (Brent et al. 2008).

Although pharmacoepidemiological data do not indicate an association between antidepressant use and completed suicide (Henry et al. 2012), the regulators in the USA (FDA) and Europe (EMA) both reacted to reports of a possible link by trying to restrict the use of antidepressants in children and adolescents. This involved issuing "black box" warnings that aimed at restricting the use of these drugs to severe cases that have not responded to psychotherapy. The impact of the "black box" warnings continues to be debated. While Gibbons et al. (2007) reported that subsequent decreases in SSRI use were associated with an increase in suicide in adolescents following the issue of the warnings, Sparks and Duncan (2013) suggest that, overall, pediatric antidepressant prescriptions did not decline significantly and that while rates of youth suicide did rise, this increase has only been seen in more recent years. In view of ecological data from adult studies conducted across 29 European countries which suggests that increased SSRI use is generally linked to lower suicide rates (Gusmao et al. 2013) and direct trial evidence that SSRIs do not increase suicidality (Brent et al. 2008), we conclude that the potential benefits of SSRIs for treating depression in adolescence outweigh the risks.

Medication Treatments for Anxiety

Treatment of anxiety disorders in children and adolescent with medications is also contentious. Although it is acknowledged that the success rates for cognitive and behavioral interventions are relatively high (70–80%), this still leaves a significant proportion of anxious children and adolescents requiring further intervention. Notwithstanding this, there is no provision for the use of medication within the UK NICE guidelines for managing anxiety in children and adolescents (Nice 2013). In the USA, the AACAP practice parameters also recommend CBT as the first-line therapy for most cases but suggest that SSRIs should be considered for moderate to severe cases and those who fail to respond to psychological therapies (Connolly and Bernstein 2007). Unfortunately, there is no guidance within the AACAP practice parameters as to which medications should be considered or how they should be used.

Reviewing the evidence, it again appears that the tricyclic antidepressants should not be considered as first-line treatments for pediatric anxiety disorders (Velosa and Riddle 2000). Benzodiazepines should be considered only when other pharmacological approaches have failed, and they should be prescribed for weeks rather than months, with dose adjustments being made gradually, both when starting and when tapering off treatment (Velosa and Riddle 2000). There is some open-label evidence to suggest that buspirone, a non-benzodiazepine anxiolytic, has a similar efficacy to benzodiazepines with fewer adverse events for childhood anxiety disorders. However, no controlled data are available for either safety or efficacy.

As for depression, the SSRIs are considered the first-choice pharmacological treatment for child and adolescent anxiety disorders. There are now randomized controlled trial data supporting the efficacy and safety of fluoxetine, sertraline, fluvoxamine, paroxetine, and venlafaxine in this population. The Cochrane review by Ipser and colleagues (2009) identified 9 eligible studies with pooled treatment response rates of 64% for the active treatment vs. 34% for placebo giving an overall risk ratio of 2.01 (95% CI 1.59, 2.55) favoring treatment, a number needed to treat of 3 and a pooled effect size of 0.82. They did not identify any clear differences between the different medications. Overall, these suggest a stronger response to the SSRIs for pediatric anxiety compared to adolescent depression.

All of the studies included in the Cochrane review were short-term trials, lasting a maximum of 16 weeks and often shorter. Despite there being no clear evidence either way, concerns have been expressed about the long-term safety of SSRIs for children. Animal studies do raise the possibility of long-term negative effects on brain development. The administration of SSRIs to juvenile rodents has, in some studies, been shown to induce long-term changes in serotonergic transmission in the cortex and hippocampus. However, these concerns must be balanced against the finding that chronic stress, such as that associated with ongoing anxiety, also results in long-term unwanted changes to neurochemistry and neuronal development.

Only one clinical study has investigated long-term treatment. The Child/Adolescent Anxiety Multimodal Study (Compton et al. 2010; Walkup et al. 2008) investigated both short-term efficacy (12 weeks) and long-term persistence of effect (36 weeks) across four groups: cognitive behavioral therapy (CBT), sertraline, and combined therapy (CBT + sertraline), all of which were compared to placebo. This was a large study that included 488 children and adolescents, and as the inclusion criteria allowed for comorbidities, such as ADHD, major depression, and dysthymia, the results should generalize out to clinic populations better than for most clinical trials. The results were encouraging. 80.7% of patients receiving combined therapy had a significant improvement on CGI Improvement scale, compared to 59.7% children receiving CBT alone and 54.9% receiving sertraline. Effect sizes were 0.86 for combined therapy, 0.45 for sertraline, and 0.31 for CBT, and NNT were 2 for combined therapy, 3 for sertraline, and 3 for CBT. There were no differences in adverse event rates between sertraline- and placebo-treated groups.

In summary, it does appear that a significant proportion of anxious children and adolescents benefit from pharmacological treatments. Unfortunately, it is not yet possible to predict who will respond to either psychological or pharmacological

treatments in these children and adolescents. When using medication, the SSRIs should be seen as the first-line treatment for anxiety disorders in children and adolescents. Clinicians should allow at least 3 weeks, at an adequate dose, before deciding if there has been a response. In cases of non-response, it would be appropriate to switch to an alternative SSRI before changing to a drug from a different class. Even where a pharmacological approach is chosen, this should usually be combined with a psychotherapeutic approach as this has been demonstrated to increase response rates and clinical improvement. Serotonin-enhancing agents such as the SSRIs and clomipramine are efficacious treatments for this disorder. The overall effect size for pharmacotherapy is medium at 0.48, and NNT is 6, with some variation between different medications (Watson and Rees 2008). These figures are similar to those reported in adults.

Medication Treatments for Obsessive–Compulsive Disorder

CBT in the form of exposure with response prevention has been demonstrated to be an effective treatment for pediatric OCD, and there is international consensus that CBT should be offered to all young people with OCD and should be the first-line treatment in mild-to-moderate cases of OCD (Geller and March 2012; Nice 2005). There is also relatively strong evidence to support the use of drug treatments for early-onset obsessive–compulsive disorder (OCD) (Watson and Rees 2008). Fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram have all been shown to be effective in the treatment of pediatric OCD; they are associated with a 29–44% reduction in symptoms and appear to be well tolerated and safe. There are few comparative treatment trials of different SSRIs and little or no evidence to suggest that any one SSRI is more effective than another. Clomipramine has also been demonstrated to be effective in pediatric OCD in several RCTs but its use is limited by concerns over safety.

Only one study to date has directly compared the efficacy of CBT versus SSRI medication in pediatric OCD (Pediatric OCD Treatment Study (POTS) Team 2004). This study found that CBT and sertraline were associated with comparable levels of symptom reduction, but that combined CBT and SSRI treatment was associated with superior outcomes. Further study by the same team has confirmed that the combination of CBT and medication is superior to medication as a monotherapy in pediatric OCD, but only if a full course of CBT is completed. The time taken to respond to SSRI treatment for OCD varies between the studies, and even though Riddle et al. (2001) reported significant responses after only 1 week of treatment, most authors suggest titration over 6–8 weeks and to continue to maximum tolerated doses in partial or non-responders.

OCD is recognized as a chronic condition that persists into early adulthood in about 50% of early-onset cases. SSRIs have been demonstrated not only to be well tolerated and effective at maintaining improvement over time but also to result in continued improvements in symptoms for up to 1 year (Cook et al. 2001; Thomsen 2000). Although treatment continued after this time appears to remain effective, it

does not seem to result in further improvements. It is not known how long treatment should be continued for. Although obsessional symptoms may relapse when treatment is discontinued, it is generally suggested to stop medication after 1–1.5 years and then restart if significant symptoms return.

In cases of non-response to medication, it is important to assess treatment compliance and to ensure that other factors, such as family discord, other psychosocial stressors, and comorbid disorders, have been adequately addressed. Earlier age of onset, longer duration of OCD, and specific symptom subtypes seem to predict a lower rate of response. Different people respond differently to particular SSRIs. It is therefore recommended that a second SSRI should be trialed if there is no response to the initial one and that this is augmented by CBT. In adults with OCD, augmentation strategies using antipsychotics have been demonstrated to be efficacious in cases of partial response. These strategies have not been studied in children and adolescents.

Medication Treatments for Tics and Tourette's

When thinking about treating tics, it is important to take into account the natural history and course of Tourette syndrome, which usually has its onset in early childhood, increases in severity at puberty, attenuates somewhat after puberty, and stabilizes in adulthood. Throughout this time, tics fluctuate in severity throughout with a periodicity of around 3 months. This waxing and waning of tics can make it very difficult to assess the effects of any treatment interventions and highlights the need for careful recording of the baseline and monitoring of symptoms, both before a new medication is started and during treatment.

Until the introduction of the second-generation antipsychotics, haloperidol, pimozide, and, in the UK, sulpiride, were the mainstay of treatment for tic disorders. All three have been shown in RCTs to be efficacious in reducing tics. Haloperidol has the strongest effect, leading to improvement in approximately two-thirds of cases, with pimozide and sulpiride improving tics in just over one-half. However, all three are associated with frequent adverse reactions. For haloperidol, the main concerns are the often disabling extrapyramidal effects. Pimozide is associated with fewer adverse events than haloperidol, but can result in ECG abnormalities, particularly prolongation of the QT interval, and requires an ECG before starting treatment, repeated annually to review QT interval. Sulpiride is also associated with a lower, but not absent, rate of extrapyramidal side effects.

More recently, interest has focused on the atypical antipsychotics. As is often the case in pediatric psychopharmacology, their increased use outstripped the available evidence. There are however now several RCTs supporting short-term efficacy, although longer-term safety data are still not available. Trial data support ziprasidone (at a dose of 30 mg/day) (Sallee et al. 2000), risperidone (2.5–3.5 mg/day) (Dion et al. 2002; Zhao and Zhu 2003), and olanzapine (Ji et al. 2005; Onofrj et al. 2000). Although several authorities now suggest that aripiprazole should be considered the first-line medication in case of moderate tics, in doses of 1–5 mg/day, with the

possibility of higher doses in more severe cases, there are as yet no RCT data to back up this position.

It has been suggested that atypical antipsychotics may benefit those with tic disorders because they are having a positive effect on general functioning by improving emotional and behavioral symptoms as well as tics. There is however no real evidence to support this suggestion (nor to refute it). While clinical experience suggests that many patients do benefit from atypicals, a significant number are unhappy about adverse effects, particularly weight gain and metabolic disturbances. They have, however, for many clinicians become the first-line treatment for tics. This reflects not only their efficacy in reducing tics but also their impact on other target symptoms, such as ADHD, OCD, and aggression. It is essential when discussing medication for tics with a patient and their family to have a frank and honest discussion about the risk/benefit balance and to allow them time to weigh this up before committing to a firm decision.

Clearly, not everyone with tics requires or wishes for a medication treatments. The European Society for the Study of Tourette Syndrome (ESSTS) guidelines (Roessner et al. 2011) suggest that medication should be considered when tics cause:

- Subjective discomfort (e.g., pain or injury)
- Sustained social problems for the patient (e.g., social isolation or bullying)
- Social and emotional problems for the patient (e.g., reactive depressive symptoms)
- Functional interference (e.g., impairment of academic achievements)

Although, compared with the antipsychotics, the evidence to support the efficacy of clonidine for the management of TS is less robust, clonidine (and possibly guanfacine) may also improve ADHD symptoms alongside suppression of mild-to-moderate tics. In addition, clonidine tends to alleviate initial insomnia and reduce anxiety (Sandor 1995). While other medications have been studied and are sometimes used in clinical practice, the evidence for their efficacy is limited and often contradictory. Studies on a wide range of other medications are helpfully summarized by Hartmann and Worbe (2013).

Medication Treatments for Autism Spectrum Disorder (ASD)

There are currently no recognized treatments for the core symptoms of ASD, and proposed treatments mostly focus on associated troublesome behaviors and comorbid disorders (Simonoff et al. 2008). The most common targets for treatment are self-injurious behavior, aggression to others or objects and property, tantrums, yelling/screaming, stereotypies, hyperactivity, impulsivity, and agitation. The use of medications to treat these behaviors is now common notwithstanding the fact that the evidence for efficacy and safety remains sparse. It is however important for clinicians to maintain a working knowledge of what has been studied which can help greatly when planning clinical work. It is however also essential that clinicians think

about possible non-pharmacological interventions before reaching for the prescription pad.

For many individuals with ASD, irritability and aggression are among the most impairing symptoms. They are also the best studied with respect to pharmacological interventions. Various antipsychotics, mood stabilizers, antidepressants (clomipramine), and other agents (clonidine, amantadine, naltrexone, pentoxifylline) have been investigated for reduction of irritability in the context of ASD. Irritability is in fact the only symptom for which there are medications approved for use in ASD, although only in the USA (risperidone from 2006 and aripiprazole from 2009). Risperidone received an indication for children over 5 years of age and a body weight of $\geq$9.1 kg and aripiprazole to children older than 6 years. The effect size is around 1.2 for risperidone (0.5–3.5 mg/day) and 0.6–0.9 for aripiprazole (5, 10, 15 mg/day). Extrapyramidal side effects, weight gain, dizziness, and somnolence are the most important adverse effects associated with these medications. The positive effects on irritability and aggression do not appear to be secondary to somnolence.

Of the drugs prescribed offlabel, valproic acid (sodium valproate) in doses resulting in blood valproate levels of 87–110 mcg/ml has been shown to reduce irritability scores on the Clinical Global Impression (CGI) irritability subscale in a majority (62.5%) of children and adolescents with autism spectrum disorders and result in statistically significant improvements in scores on the irritability subscale of the Aberrant Behavior Checklist (Hollander et al. 2010). Valproate is associated with significant risks to the unborn baby when administered during pregnancy. For this reason, it is strongly advised that it is not prescribed to women and girls of childbearing age. While there is some emerging data to suggest that lurasidone may also have some efficacy in reducing irritability, the findings are not yet conclusive. It may however be a reasonable alternative, before haloperidol and ziprasidone, for those who experience tolerability issues with risperidone and aripiprazole or whose symptoms are refractory to these drugs (Mcclellan et al. 2017).

The management of ADHD symptoms in ASD has not been studied extensively (Bratt et al. 2017), but the limited available evidence suggests that (1) treatment should be similar to that for routine cases of ADHD; (2) the effect sizes are somewhat lower than those seen in children and adolescents with ADHD without ASD (i.e., they are only moderate for stimulant medications); and (3) adverse effects are more likely in the group with ADHD and ASD. The maxim of "start low and go slow" should be applied when prescribing any medications for ADHD in children and young people with ASD and medication doses increased with caution.

Antipsychotics, antidepressants, and mood stabilizers have all been investigated as potential treatments for the reduction of stereotypies and repetitive behaviors in children and adolescents with ASD. Randomized controlled trials of aripiprazole (Marcus et al. 2009; Owen et al. 2009) and risperidone (Mcdougle et al. 2005) both reported significant improvement in more than 50% of study participants. Statistically but not clinically significant response has also been reported for fluoxetine and valproic acid (Hollander et al. 2005, 2010), haloperidol, and clomipramine (Remington et al. 2001). Modest improvements of stereotyped behaviors following treatment with guanfacine have been reported (Politte et al. 2018).

Medication Treatments for Bipolar Disorder

Recent controversies around the diagnosis of bipolar II (BP II) and "bipolar disorder not otherwise specified (BP-NOS)" have subsided somewhat with the recognition that many young people who were receiving one of these diagnoses were in fact presenting with ADHD combined with mood lability or what is now termed disruptive mood dysregulation disorder (DMDD). We agree with the UK NICE that the diagnoses of BP II and BP-NOS should be reserved for adults but acknowledge that bipolar 1 (BP I) is a valid, if uncommon, diagnosis in adolescents and rare but possible in childhood.

Medication treatments are most often considered as an essential component of a treatment package for BP 1 in children and adolescents. Liu et al. (2011) systematically reviewed pharmacological approaches to the treatment of bipolar in children and adolescents. They identified 29 open label and 17 RCTs. The overall odds ratio of 2.23 was significantly greater than 1. Much of the effects were accounted for by the highly significant effects for the second-generation antipsychotics. There were positive RCTs for aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. The meta-analysis effects were not significant for divalproex (sodium valproate) and only mildly positive for topiramate and oxcarbazepine (a derivative of carbamazepine). As noted above, sodium valproate should be avoided in girls and women of childbearing age. Although there is some evidence that lithium is also effective in treating BP I in children and adolescents, this evidence is low in quality and findings are mixed. The FDA has indicated that risperidone, quetiapine, and aripiprazole can be used in bipolar disorder for children aged 10 and over, lithium for children over 12, and olanzapine for children over 13 years.

Lurasidone, an atypical antipsychotic, has recently been awarded a license in the USA for the treatment of bipolar depression in adolescents aged 10–17 years in doses between 20 and 40 mg (Channing et al. 2018; Delbello et al. 2017). Clinical trial data and recently reported longer-term follow-up studies have suggested that, in this population, lurasidone is associated with minimal impact on weight gain and metabolic markers.

Medication Treatments for Schizophrenia

Early-onset schizophrenia, the development of psychotic symptoms before the age of 18 years, is associated with severe functional impairments and poor outcomes. Medications have a key role in treating early-onset schizophrenia but caution is required, both because of the potential for serious adverse effects and because, if used too early, they can blur the clinical picture making an already complex diagnostic process even more difficult. In this respect, antipsychotic medication should not be started until a clear diagnosis has been made – and then for those meeting definite criteria for schizophrenia and not those with less clear and more nebulous states of false thinking. It is also important to remember that pharmacological treatments should always be given within the context of a multidisciplinary team able to offer a broad range of supportive therapies.

Despite considerable evidence of efficacy and effectiveness of multiple antipsychotics both typical and atypical in adult schizophrenia, very few studies have included children or young people. The introduction of new legislation for both the FDA and EMA has meant that the makers of recently developed antipsychotics have had to include adolescent clinical data in their submissions to the regulators. As a consequence, we will start to see more studies being conducted. Lurasidone has been through this process and is now licensed in several countries as a treatment for adolescent schizophrenia. The data available includes short-term RCH, a randomized withdrawal study demonstrating longer-term efficacy, and a 2-year open-label study focusing on safety and tolerability (Channing et al. 2018).

Despite the lack of evidence for many of the antipsychotics, the evidence that is available suggests considerable continuity in drug response between early- and adult-onset schizophrenia. Research in both adults and children suggests that almost all antipsychotic medications are of similar efficacy and result in similar rates and patterns of symptom reduction. The main effects center on reduction in positive symptoms, while effects on negative symptoms are relatively minor. As a consequence, it is the adverse effects profile that has the biggest influence on clinical decision-making (Table 2).

With respect to monitoring adverse effects when using antipsychotic medications in children and adolescents (for any clinical indication), it is wise to follow the recommendation from the NICE schizophrenia guidelines. At baseline, before starting any antipsychotic, NICE recommend measuring: weight and height (and plotting these on a growth chart); waist and hip circumference; pulse and blood pressure; blood glucose; glycosylated hemoglobin (HbA1c), blood lipid profile and prolactin levels; assessing any movement disorders; assessing nutritional status, diet, and level of physical activity; and performing an ECG. Efficacy, together with a safety assessment, similar to baseline investigations, should be repeated systematically during the treatment according to the following scheme: weight, weekly for the first 6 weeks, at 12 weeks, and then every 6 months (plotted on a growth chart), height every 6 months (plotted on a growth chart), waist and hip circumference every 6 months (plotted on a percentile chart), pulse and blood pressure (plotted on a percentile chart) at 12 weeks and then every 6 months, and fasting blood glucose, HbA1c, blood lipid, and prolactin levels at 12 weeks and then every 6 months. These should be repeated periodically and abnormal results of negative changes should be acted on.

It is usual to ensure that the patient has had an adequate trial (6 weeks) at an adequate dose. If there is no response after this time, a different antipsychotic should be tried. For treatment-resistant schizophrenia, clozapine is acknowledged as the most effective medication in adults. Although there is relatively little evidence for clozapine in children and adolescents, there is some suggesting that clozapine may be more efficacious than haloperidol (Kumra 2000) and olanzapine (Kumra et al. 2008) at treating both positive and negative symptoms. However, serious adverse effects including neutropenia and seizures are relatively common and require close monitoring and regular blood testing. Clozapine should be reserved for patients who have failed to respond to at least two adequate trials of other antipsychotic agents, at

Table 2 Adverse effect profiles of haloperidol and second-generation antipsychotics in children and adolescents

Adverse effect	Time of onset	Haloperidol	Aripiprazole	Clozapine	Olanzapine	Quetiapine	Risperidone	Ziprasidone	Lurasidone
Anticholinergic	Early	–	–	+++	++	–/+	–	–	–
Acute parkinsonism	Early	+++	+	–	+	–	++	+	++
Akathisia	Early/ intermediate	+++	++	+	+	+	+	+	++
Tardive dyskinesia	Late	++	–/+	–	–/+	–/+	–/+	–/+	–/+
Withdrawal dyskinesia	During switch	++	++	–	–/+	–/+	+	+	–/+
Diabetes	Late	–/+	–/+	+++	+++	++	+	–/+	–
Increased lipids	Early/ intermediate	–/+	–/+	++	++	+	+	–/+	–/+
Weight gain	Intermediate	+	+	+++	+++	++	++	+	–
Increased prolactin/ sexual dysfunction	Early	++	–	–	++	–	+++	+	–
Decreased prolactin	Early	–	++	–	–	–	–	–	–
Sedation	Early	–/+	–/+	+++	++	++	+	–/+	++
Increased QTc	Throughout	–/+	–/+	+	–/+	+	+	++	–/+
Postural hypotension	Early	–	+/–	+++	++	++	+	–	–/+
Neutropenia	Early/ intermediate	–/+	–/+	++	–/+	–/+	–/+	–/+	–/+

– = not present, –/+ = minimal, + = mild, ++ = moderate, +++ = severe

least one of which was an atypical, or who have experienced significant drug-induced side effects (e.g., tardive dyskinesia).

Managing Adverse Effects

Although child and adolescent mental clinicians are improving in their use of structured outcomes to track treatment response, the use of structured approaches to the measurement of adverse effects is still rather limited with few tools suitable for use in routine clinical practice available. As medications are used more frequently and for longer duration, accurate measurement of adverse events becomes even more important. The issues can be exemplified by the increased use of antipsychotics to manage nonpsychotic disorders such as aggressive behaviors associated with autism, intellectual disability, ADHD, and conduct disorder. At the time of starting, there is often an intention that this will be a brief intervention, but the absence of a planned exit strategy often leads to treatment over a much longer period of time. Although more recent medications are associated with less extrapyramidal side effects than some of the older typical antipsychotics, in particular haloperidol, the prevalence of obesity, diabetes mellitus, and metabolic and cardiovascular side effects is considerably higher in younger patients than they are in adults (Fraguas et al. 2011). Developmental factors also increase the impact of certain adverse events. For example, hypogonadism that can occur secondary to raised prolactin levels may have a more serious long-term impact on younger people who have not yet reached peak bone density (Haddad and Wieck 2004).

A greater effort by both clinicians and researchers to improve the routine measurement at baseline and follow up for all children and young people on psychotropic medication, and on managing adverse events when they do actually occur, is required to ensure safe practice and to improve the lives of those we treat.

Conclusions

Psychological and psychosocial therapies remain the first-line treatments for many child and adolescent mental health disorders and are an important component of a comprehensive treatment package for others. It is important, however, that clinicians develop an understanding of the potential role which medication can play, especially when psychological treatments have been unsuccessful in reducing symptoms adequately. It is however also necessary to recognize the limitations of the current evidence and to alert patients and their families of these uncertainties when suggesting the use of medication, particularly when this use goes beyond the evidence base. More high-quality treatment trials are required. This will require collaboration between academics and clinicians across a wide range of settings and also support from funding bodies and managers within health care, who need to ensure that these studies are recognized as an essential component of health-care provision.

Box 1 Questions to Ask Before Switching Medications or Adding an Additional One

1. Have I titrated properly?
2. Is the patient at the maximum dose?
3. Is this drug/preparation working well at any times during the day and do I need to change the dose or preparation to get a more balanced effect? – Particularly relevant for stimulant drugs in ADHD
4. Am I targeting the right symptoms?
5. Is there a behavioral explanation for the drug "wearing off" or is the patient becoming tolerant to this medication?
6. What else is going on in patient's life/family life, and are there non-pharmacological reasons for poor response?
7. Is the medication working but effects limited by side effects and if so can I manage this a different way?
8. Have I missed any comorbidity?
9. Is the diagnosis right?

Cross-References

► Services for Neurodevelopmental Disorders such as Autism Spectrum, Attention Deficit Hyperactivity Disorder (ADHD), and Tic Disorders

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