

Adverse effects of medication

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Abstract

The commonest adverse effects of methylphenidate and dexamfetamine are appetite suppression, weight loss and sleep disturbance, although sometimes sleep is improved. There can be a modest effect of stimulant medication on decreasing growth velocity, but even this can be avoided by regular monitoring and adjustment of dosage or preparation when needed. Tics are not a contraindication to stimulant medication but exacerbation of tics may warrant dose reduction or change of medication. Both stimulant medication and atomoxetine can increase blood pressure, but any increases are usually small. The risk of sudden death does not appear to be increased by stimulant medication. Routine ECGs are not recommended. Specialist opinion should, however, be sought before medication is commenced for patients with a relevant personal or family cardiac history. Baseline measurement and regular follow-up monitoring of blood pressure, pulse, height (in children) and weight are recommended for patients taking stimulant medication or atomoxetine. The potential for substance misuse is probably not increased by prescribing medication for ADHD. Psychotic symptoms are only rarely associated with ADHD treatment. Most of the adverse effects of licensed medication for ADHD are mild and/or easily reversible.

Introduction

Because millions of patients have been treated with stimulant medication, which has been prescribed for several decades, the adverse effects are well known. Methylphenidate, dexamfetamine and atomoxetine are licensed and widely used in the UK for the treatment of ADHD in children. They are also useful and authoritatively recommended for treating adults even though no marketing licences are in place (except for atomoxetine, provided treatment was started in childhood). Adverse effects need to be prevented and managed. This article considers their prevalence and recommends actions for prescribers.

Neurological effects

Most adverse neurological effects are mild and/or temporary: headache and dizziness in the early stages of treatment will often disappear without any particular action or simply by dosage reduction for a period.

Insomnia is quite common in children with ADHD who are not medicated (1). Studies comparing medicated and un-medicated children describe inconsistent outcomes, both for polysomnographic measures and for parental reports (2). It is only to be expected that stimulants will stimulate, but the short action of most stimulants means that most of the effect has disappeared by bedtime. Furthermore, for some children falling asleep may be a problem in self-regulation that stimulant drugs may actually help.

The initial management will probably be by advising sleep hygiene, behaviour therapy techniques based on stimulus control, and appropriate bed-time scheduling. Adjusting the timing of doses is often effective; eg switching from a long-acting drug (such as Concerta XL) to a shorter-acting preparation of medication (such as Equasym XL, Ritalin LA, Medikinet or immediate-release methylphenidate).

The next step will be to consider a change of medication. Atomoxetine does not usually disturb sleep, and in one study (2) was shown to be more helpful for sleep than methylphenidate. Clonidine, which has both sedative and anti-hyperactivity actions, can be effective in ADHD with associated sleep problems (3). Melatonin has trial evidence to support its use in reducing sleep-onset problems in ADHD children (4), and is probably the most widely used add-on for this purpose in the UK.

Tics are quite common in un-medicated people with ADHD (5). Some formularies still present a contraindication for the use of stimulants in patients with Tourette Disorder (5,6), and even for people who only have a family history of tics, but this is outdated. Recent reviews (7,8,9) indicate that stimulants do not cause de novo Tourette, and “should not be disregarded” when planning treatment for ADHD in the presence of tics.

On the other hand, a few people with established tics (about 5-10%) may show an exacerbation with stimulants. The natural history of tics is to fluctuate, so a rapid reaction by the prescriber is not usually the best way to go. An increase due to stimulants will be reversible with withdrawal or dose reduction of the drug and in any case may be seen as a price worth paying for good ADHD control. Atomoxetine does not worsen tics and may even improve them, so is often helpful (10,11,12). Clonidine has some action in reducing tics, and has some anti-hyperactivity action when in combination with methylphenidate; so it can be a useful add-on medication (13).

Epilepsy is not a contraindication to anti-hyperactivity medication. There are occasionally concerns that, as with other psychotropics, ADHD medications may lower the seizure threshold so as to cause seizures in previously seizure-free individuals. However, in prospective trials, retrospective cohort studies and postmarketing surveillance in ADHD patients without epilepsies, the incidence of seizures did not differ between ADHD pharmacotherapy and placebo (relative risk for current vs non-use for methylphenidate: 0.8; for atomoxetine: 1.1) (14,15)

Cardiovascular adverse events

CNS Stimulants can increase both blood pressure (average increases 1 to 4 mm Hg systolic and 1 to 2 mm Hg diastolic) (16) and heart rate (1-2 beats per minute) (17,16). While such small changes seem trivial, they can imply an increase in the number of children at the extreme end of the scale. The risk from hypertension is considered to need intervention when the blood pressure exceeds the 95th centile. The initial evaluation and monitoring of blood pressure should therefore be recorded on centile charts. Normative charts are available for several countries (18,19,20), so local norms should be used wherever possible. Monitoring of blood pressure and heart rate should be at least 6-monthly; and in any case after dose increases. If the first recording is elevated, then it should be repeated at least twice and if still elevated, and above the 95th centile, then a dose reduction or drug holiday should clarify whether the drug is responsible. If the blood pressure remains high, then referral to a paediatric hypertension specialist is required, for 24-hour ambulatory blood pressure recordings to confirm the diagnosis and to initiate any investigations for end organ damage. If the blood pressure has come down to normal, implying that the drug is responsible, then the options available include reverting to non-pharmacological management of hyperactivity, which is not always successful, or switching medication. However, other drugs may well have the same effect. Specialist paediatric consultation is advised; the outcome may include continuing medication with the addition of an antihypertensive (clonidine being an obvious choice).

Routine ECG monitoring is not required for children on stimulant medication or atomoxetine. The biggest fear has been that there might be a risk for sudden death. Epidemiological surveillance, however, has indicated that otherwise unexplained sudden death is extremely rare in the medicated population – so rare, indeed, that it is very hard to tell whether it is any commoner than in the general population of children (where the rate is approximately 1.2 to 1.3/100,000/yr) (21,22,23,24,25) 25 sudden deaths were identified by the FDA in individuals prescribed ADHD medications, corresponding to a low figure of 0.2-0.5/100,000/year (21). This does not, of course, mean that the anti-hyperactivity drugs are protective against sudden death. It is very possible that there is under-reporting – a rule of thumb is that about 50% of major adverse effects are not reported, but there is much room for uncertainty.

The average QTc interval is not changed significantly by methylphenidate, amphetamine salts or atomoxetine. If there is a risk in the individual case (e.g. in a patient known to show the congenital long-QT syndrome), then detailed discussion and a cardiological opinion should guide practice. In summary, pre-treatment cardiovascular screening should include any known cardiac problem, a history of cardiac symptoms (e.g. arrhythmias, or undue breathlessness, or syncope on exercise), a positive family history of sudden death below the age of 40 years, and measurement of blood pressure and heart rate.

Self-injury

Suicidal thinking was found to be a little more common among children and adolescents treated with atomoxetine (5/1357) compared to those treated with placebo (0/851) in clinical trials. This implied a number needed to harm (NNH) of 227, compared to the number needed to treat (NNT) of 5, to achieve remission of ADHD symptoms (26). The evidence for stimulants is less clear, so, as a precaution, they too should be seen as carrying a small risk. Families and caregivers should be advised of the need to recognize any emergence of emotional change or self-injurious thinking; and to communicate well with the prescriber (27).

Adverse effects on growth

On average, the reduction in height amounts to approximately 1 cm/year during the first 1-3 years of treatment (28). The reduction in weight gain appears to be somewhat more pronounced than that for height (over a 3-year period about 3 kg less than predicted) (29,30).

Small effects were seen for atomoxetine during the first 2 years of treatment; but in those who received prolonged treatment for up to 5 years, no long-term effects on growth were apparent, apart from an overweight subgroup (31,32).

Patients and their parents should therefore be told about the potential for growth suppression. A 1-year height velocity >2 SDs below the mean, or a 2-year height velocity >1.5 SDs below the mean would trigger particular concern. Nevertheless, the use of a growth chart (eg 6-monthly) should detect any early signs of growth slowing (33). Symptomatic measures would include adjusting the timing of doses (e.g. taking the first dose after breakfast) and meals (e.g., late evening meal) and encouraging the use of high-energy, nutritious snacks. Drug holidays usually seem to allow children to return to their normal growth trajectory.

Substance abuse and psychotic symptoms

Stimulants can be misused to achieve a 'high' (by injection or inhalation, not ordinarily by the oral route) or for other reasons, such as to aid weight loss, improve studying, or manage without sleep (34,35).

Whether stimulant medication adds to the risk for substance abuse is not clear; several studies suggest it does not. A meta-analytic review of six studies suggested that stimulant therapy in childhood may be associated with a reduction in risk, compared to un-medicated ADHD subjects, for subsequent drug and alcohol use disorders (36). The reduction in risk might be attributable to treatment rather than stimulant medication in particular: the follow-up of a large clinical trial found a reduction in risk for those patients treated with behaviour therapy; medication had no effect one way or the other (37). Euphoric properties and reinforcing effects of methylphenidate are associated only with intravenous injection or nasal inhalation and not with oral administration (38). Misuse or diversion of stimulants has been reported in adolescents and young adults in North America, usually in order to improve academic performance (studying, staying awake, improved alertness) (39,40,41).

Depending on the specific situation, current or previous substance abuse in the family should be seen as either a relative contraindication for stimulant prescription, (especially in the immediate

release preparation), or as a reason for particularly close monitoring of a patient's stimulant use. The extended-release formulations of stimulants are less prone to diversion because these preparations cannot easily be crushed into powder for injection or snorting, and also because the once-a-day administration makes parental supervision easier to enforce. On the evidence of preclinical data and short-term clinical and abuse liability studies, atomoxetine does not appear to be associated with risk for substance use disorders, and may well be preferred in high-risk cases (42).

Use of cannabis is not necessarily a contraindication to prescribing stimulant medication, and a pragmatic approach will be required. The other dangers of cannabis, however, should not be ignored and patients will need to be warned of these. Cocaine, however, is likely to be a real hazard in view of its sharing neurochemical effects with dopaminergic drugs, and the two should not be combined. Psychotic symptoms are only rarely associated with ADHD drug treatment. The United States Food and Drugs Administration reviewed 49 RCTs of ADHD drugs in children and found a total of 11 psychosis/mania events during 743 person years of exposure with ADHD drug treatment, compared to no psychosis events reported with placebo (43). If psychotic symptoms occur, the medication should be stopped and an urgent referral to the specialist should be made.

Conclusions

The licensed medications for ADHD should be considered as low-risk, and safer than other psychotropic drugs. For most cases, monitoring of blood pressure, pulse rate, and growth in height and weight, will be sufficient in primary care. Shared care with a specialist service should be developed for the regulation of dose and psychological effects, and for management of any of the uncommon adverse events described in this paper. A recent, full review of adverse events has been published by a European Guidelines Group (44), and is recommended for further reading. The author, who was a member of the group, has drawn on his colleagues' work, and gratefully acknowledges their systematic research.

GP Comment.

What have I learned from this paper?

1. Appetite suppression, weight loss, sleep disturbance, small increases in blood pressure and pulse, and some effects on growth can occur with medication used to treat ADHD but these adverse effects are usually mild and/or easily reversible.
2. In keeping with NICE guidelines, height, weight, blood pressure and pulse should be monitored regularly.
3. The "side effects" of some medications may be helpful; for example, clonidine used to treat ADHD may also assist with sleep disturbance.
4. Previous concerns about risk of sudden death with ADHD treatment have not been confirmed.
5. The evidence suggests that the risk of substance misuse is not increased by medications for ADHD.
6. Overall, it would appear that the recommended medication used to treat ADHD is associated with a low risk of any serious adverse effects.

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