Other Medications of Use in ADHD

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Abstract

Perhaps as many as 20% of individuals with ADHD will not respond adequately to the three medications recommended in the current NICE guideline. This paper considers treatments that are not recommended in the guideline but appear to be useful in the treatment of ADHD. The "effect size" and "common language effect size" (CLES) are defined and are quoted where data is available, as a guide to choosing effective alternatives. The alternative medications considered include clonidine, atypical antipsychotics, antidepressants, modafinil, and amantadine.

Introduction

The NICE guideline recommends only methylphenidate, atomoxetine and dexamfetamine as pharmaceutical treatments for ADHD. However, as the effect sizes suggest, as many as 20% of children needing treatment for ADHD will not respond sufficiently to these alone. This paper covers other drugs which have shown promise in the treatment of ADHD.

"Effect Size" and "Common Language Effect Size" (CLES) are standard measures used to evaluate the efficacy of drugs and will be quoted in this paper where the data is available. These terms are defined in the Appendix. However, effect sizes are not sufficient in themselves. The literature that generates them needs to be combined with professional skill in order to choose the best alternative or addition. Below are some rules of thumb, which should ensure that a clinician is able to employ both professional skill and the literature available in the most effective manner.

1. Ensure that the prescribed medications are actually being taken.

2. Prescribe guideline drugs at sufficient dosage and for sufficient duration. This is particularly important for atomoxetine, which can take several weeks to become fully effective.

3. Hunt for comorbidity. Psychiatric comorbidity is common in people with ADHD (1). (See other papers on comorbidity in this issue.) Adding a drug to treat a comorbid condition, or changing to a drug or dosage which treats it, might improve effectiveness.

4. Consider "trailing edge" technology. Older drugs often have better understood adverse-effect profiles; the commercial pressures to gain a return on investment will be less, and there will be a longer period for evidence to accumulate.

5. Unless comorbidity suggests otherwise, try switching drugs before combining drugs. Both on empirical and theoretical grounds, adverse effects are more likely with multiple drugs, and there is no empirical evidence to prefer combinations.

6. Do not disregard adding further psychological interventions if initial physical interventions are insufficient; empirical evidence suggests they can add effectiveness, particularly in the presence of comorbidity (2,3).

7. Guidance is expensive and time-consuming to produce, and so is updated infrequently. Therefore, it is reasonable to investigate drugs which have been approved for use in other jurisdictions. The American FDA have stringent and transparent approval processes, enabling reasonable assessment of efficacy.

Alternative drugs approved elsewhere

The alpha-2 adrenergic agonists, clonidine and guanfacine, have both been licensed for ADHD by the American FDA. Clonidine has been used for some time as an adjuvant to stimulants, particularly when the symptoms of ADHD have been associated with severe temper outbursts or tics (4), although the use of this combination waned when safety concerns emerged (5). The concern about cardiovascular safety has been challenged (6) and it would appear that there is no basis for this in individuals who do not have pre-existing cardiac problems. Some practitioners recommend an ECG before treating with a combination of methylphenidate and clonidine or even before treating with clonidine without methylphenidate. Subsequently, clonidine began to be used alone for sleep disorders (7) and was suggested as a first-line treatment for ADHD in the presence of tics (8). It has been evaluated, in a new long-acting form, for treatment of ADHD, where the estimated effect size for dosage up to 0.4mg/day was between .7 and .8 (CLES .69 – .71) (9). Patches have been trialled for tic therapy, and no additional safety issues have emerged (10). The long-acting versions are not available as part of the British formulary but the half-life of clonidine is typically 12-16 or more hours in adults and, in practice, twice daily administration appears to be satisfactory in children. There is a theoretical risk of rebound hypertension if doses are missed; this has not been formally evaluated but the usual advice is to avoid stopping clonidine suddenly because of the potential risk of a sudden rise in blood pressure. The drug has "orphan" status in relation to Fragile X syndrome. Guanfacine is similar to clonidine, except that its half-life is 18 hours, giving it a longer duration of action and possibly less susceptibility to rebound hypertension, though the risk theoretically remains. A long-acting preparation is now available to provide 24 hour cover and has been trialled for ADHD. It demonstrated an effect size of between .62 and .89 (CLES .66 – .74) (11,12), with insignificant adverse effects reported so far.

A second rational choice would be drugs shown to be useful in other disorders, which have been found to have efficacy in ADHD. Table details the effect sizes of the major classes of these drugs.

Table : Effect sizes and Common Language Effect Sizes on ADHD for medications used in other disorders (13)

Medication class	*EFFECT SIZE*	*CLES*
SSRIS FOR OBSESSIVE-COMPULSIVE DISORDER OR DEPRESSION	.5	.64
ANTIDEPRESSANTS FOR GENERALIZED ANXIETY DISORDER	.39	.61
ATYPICAL ANTIPSYCHOTIC DRUGS* FOR SCHIZOPHRENIA	.25	.57

*OLANZAPINE, QUETIAPINE, RISPERIDONE, AND SERTINDOLE

19% of children with ADHD are reported as having comorbid anxiety and 14% comorbid depression (14); given that inattention is an important symptom for both these disorders, the effect sizes quoted above may underestimate the impact of effective treatment of these comorbidities.

Antipsychotics are valuable for mood dysregulation, aggression and irritability, which are frequently comorbid with, but not diagnostic of, ADHD, implying that these drugs are likely to be valuable for augmenting first-line treatments in the presence of comorbidity. Risperidone appears to be particularly valuable in reducing anxiety and behavioural problems in children with learning disability and autism spectrum disorder; as a result, it may also decrease some of the characteristics associated with ADHD in these children. McCracken et al., in a randomised, double-blind, placebo-controlled trial demonstrated reductions in irritability ($p<0.001$), tantrums, aggression and self-injurious behaviour in children with autistic disorder treated with risperidone. Aripiprazole is also being used for this indication, although the evidence is relatively sparse.

[1] A drug is said to be "orphaned" when a possible indication for a rare disorder exists, but the likely returns on investment are deemed too small to allow a commercial development programme

Tricyclic antidepressants and buspirone have an anti-hyperactivity effect; however, the adverse effects associated with these drugs have resulted in very limited current use. They might be considered if licensed medications have failed or have been unacceptable.

Modafinil is not related to any of the drugs already discussed. It is used to treat narcolepsy but several studies found it to be effective in ADHD, with an effect size of 0.69 – 1.08 (CLES 0.69 – 0.76). There has been concern about reports of skin rashes, with the unconfirmed possibility of Stevens-Johnson syndrome. However, all the skin rashes reported resolved without sequelae, and not all were unequivocally related to modafinil. Aggression has also been reported as being a problem in around 2%. The decision not to develop modafinil further as a treatment for ADHD was taken by the drug company, rather than regulatory agencies, who had merely asked for more data. It may remain a possibility for difficult-to-treat ADHD, although it might be advisable to escalate the dose slowly and to monitor the patient closely because of the possible risk of skin rash (15).

Finally, amantadine has the advantages of a long history and a well-understood adverse-effect profile; it is better known for its use in post-traumatic attentional states (16) but may also be of benefit in ADHD (17). The single randomised controlled trial undertaken, an equivalence study with methylphenidate, does not allow estimate of effect size.

Alternative formulations approved elsewhere

Though not licensed in the UK, methylphenidate is also available as a transdermal patch; it has shown good acceptability, equivalent effectiveness to oral delivery methods (18) and possibly some advantages for the child's quality of life (19). It is clearly of use for children who have difficulty swallowing tablets.

Though amphetamine is of equivalent efficacy to methylphenidate, and with a slightly worse adverse effect profile overall (20), nonetheless individuals may respond differently to amphetamine from methylphenidate, allowing a switch within the most effective class of medication for treating ADHD. While long-acting amphetamine preparations are not licensed in the UK, oral long-acting preparations have received FDA approval (21), and offer a potential alternative without requiring frequent dosage. Lisdexamfetamine is an interesting formulation of dexamfetamine because it is said to be active only when taken by mouth; this avoids the likelihood of "diversion" into intravenous or inhaled use. It has been approved by the FDA and there has been some recent activity to obtain European approval.

Conclusion

There is evidence that some drugs not recommended in the NICE guideline may nevertheless be effective and these should be considered if the child with ADHD has not responded to the standard drugs. However, before changing medication, the whole situation, including issues such as social factors, compliance and appropriate dosage, should be re-assessed carefully.

Appendix.

Definitions of "Effect Size" and "Common Language Effect Size" (CLES).

Effect size is the difference between two means (generally of the treatment group and placebo group) divided by the standard deviation of what is being measured. Effect sizes of around 0.2 are considered "small"; 0.5 "moderate" and 0.8 "large" (3). However, this figure disguises the proportion of cases in the treatment group which have not improved relative to the control group. The equivalent "Common Language Effect Size" (CLES) is defined as the probability that a person selected at random from the treatment group will have a higher score than that of the control group (4). It can be thought of as the likelihood that a "typical" patient who is treated will be better than a "typical" patient remaining untreated. A CLES of .5 means that treated and untreated groups will have a similar proportion of patients getting better (Definition adapted from Wikipedia.)

GP Comment.

What have I learned from this paper?

1. Methylphenidate, dexamfetamine and atomoxetine are recommended by the NICE ADHD guideline but are not always effective or may have unacceptable adverse effects, implying that other medication may be required.

2. There is reasonable evidence for a positive effect of clonidine in ADHD and it can be particularly helpful in individuals who have sleep disturbance; however, it should not be stopped suddenly because of the theoretical risk of rebound high blood pressure.

3. There is good evidence for reduction of irritability, anxiety and behavioural disturbance with risperidone, particularly in young people with autism spectrum disorder, although this drug might not directly treat the core symptoms of ADHD.

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