

ADHD medications: Of all available drugs, methylphenidate should be first option for short-term treatment in children

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Of the drugs available for attention-deficit hyperactivity disorder (ADHD), the most effective and safe for short-term treatment is methylphenidate for children, and amphetamines for adults, according to the most comprehensive evidence yet from a network meta-analysis and systematic review comparing the effectiveness and safety of seven ADHD drugs against placebo, published in *The Lancet Psychiatry* journal.

The study compared the effectiveness and side effects of amphetamines (including lisdexamfetamine), atomoxetine, bupropion, clonidine, guanfacine, methylphenidate, and modafinil with each other or with placebo over 12 weeks of treatment. However, more research to confirm longer term effects of ADHD medications is urgently needed.

Although they are commonly prescribed for people with ADHD, the study did not include antipsychotic drugs or antidepressants as they do not treat ADHD core symptoms. The study also does not include psychological therapies used for ADHD, but the authors say that these should be regularly discussed with people with ADHD and their family members or carers, and possibly offered before ADHD medications, if appropriate, especially for children and adolescents.

"Medication can be an important tool for people with ADHD, and our study illustrates that in the short term, these can be effective and safe



treatment options for children, adolescents and adults," says Dr. Andrea Cipriani, University of Oxford, UK. "It's important to note that the data available only allow us to compare the effectiveness at 12 weeks, when we know that both children and adults can be on these medications for longer. More research is needed into the long-term effects of medication. Environmental modifications—such as changes made to minimise the impact of ADHD in day-to-day living—and non-pharmacological therapies should be considered first in ADHD treatment, but for people who require drug treatments, our study finds that methylphenidate should be the first drug offered for children and adolescents, and amphetamines should be the first drug offered for adults."

ADHD is estimated to affect 5% of school-age children and 2.5% of adults worldwide. The disorder is characterised by age-inappropriate levels of inattention, hyperactivity or impulsivity, or all of these. The annual costs associated with ADHD are substantial in many countries, including US\$143-266 billion in the USA.

ADHD medications are not a permanent cure for ADHD but may help patients concentrate better, be less impulsive, feel calmer, and learn and practice new skills. Treatment breaks are occasionally recommended to assess whether the medication is still needed, but the treatment for ADHD can be taken for periods longer than 12 weeks.

Over the past few decades, prescriptions for drugs for ADHD have increased in the USA and other countries, but treatment guidelines are inconsistent as there are a few head-to-head comparisons of ADHD drugs available.

Currently, the UK National Institute for Health and Care Excellence (NICE) recommends methylphenidate as first-line drug treatment in children and adolescents (with lisdexamfetamine as the second option,



and atomoxetine or guanfacine recommended as third-line drugs), and recommend methylphenidate and lisdexamfetamine as first choices in adults. Other guidelines in Europe recommend psychostimulants as first-line treatment without any distinction between methylphenidate and amphetamines being made.

This study compared the available drugs based on how effectively they reduce ADHD symptoms and improve general functioning over 12 weeks of treatment. It also studied the drugs' side effects (including blood pressure and weight loss), and acceptability was assessed according to how many people dropped out of trials for any reason.

Of the 133 randomised clinical trials included, 81 were in children and adolescents, 51 were in adults and one trial was in both. Of these, 89 randomised controlled trials included unpublished data or were completely unpublished. Drug effectiveness was reviewed in 10068 children and adolescents and in 8131 adults, while side effects were evaluated in 11018 children and adolescents and 5362 adults.

Symptom rating came from teachers and clinicians for children, and for adults these were given by clinicians.

Based on clinician ratings in children and adolescents, all drugs were more effective than placebo in controlling ADHD symptoms. But teachers only rated methylphenidate and modafinil as more effective than placebo (there was no data for teacher ratings of amphetamines and clonidine).

In adults, there was no data for guanfacine and clonidine. Clinicians rated all other drugs, except modafinil, as more effective than placebo in controlling ADHD symptoms.

Comparing all seven drugs, amphetamines were more effective than



modafinil, atomoxetine and methylphenidate in children, adolescents, and adults.

Generally, ADHD drugs were less effective and less tolerable for adults than children and adolescents, and the cause of this is unknown.

Amphetamines, methylphenidate, atomoxetine, and modafinil caused weight loss in children, adolescents and adults. Amphetamines and atomoxetine increased blood pressure in children and adolescents blood, and methylphenidate did so in adults.

In children and adolescents, methylphenidate was the only drug with better acceptability than placebo, and in adults, only amphetamines had better acceptability than placebo.

Taking all of the outcomes into account, the authors conclude that methylphenidate should be the first option drug for children and adolescents with ADHD. In adults, they conclude that amphetamines should be the first drug to be offered.

However, there was not enough evidence available to confirm whether lisdexamfetamine—which is currently recommended by NICE for adults with ADHD—was more effective and tolerable for adults with ADHD than other amphetamines available. In addition, although NICE recommends atomoxetine and guanfacine as third-line drugs in children, the study found these to be as tolerable or less tolerable than placebo.

"Our findings will hopefully help people with ADHD in the USA find the best treatment for them by clarifying which drugs should be first, second and third line treatments. With an increasing number of people being diagnosed with ADHD and given a drug prescription in the USA, our study provides a starting point for medication, and hopefully helps patients more quickly find a drug that works for them." says Dr.



Cipriani.

The authors note some limitations, including that, despite efforts to include all available trials and unpublished data, they cannot rule out missing studies. They had also planned to study the drugs over the long-term (26 and 52 weeks), but were unable to do so as there was little data available.

Dr. Cipriani continues: "The lack of randomised controlled trials with outcomes beyond 12 weeks highlights the need for research funding to assess the long-term effects of these drugs. However, the evidence we have about methylphenidate and amphetamines from our study is robust, and should help inform clinical decisions."

Writing in a linked Comment, Mark Stein, Seattle Children's Hospital, USA, says: "As diagnostic rates of attention-deficit hyperactivity disorder (ADHD) increase worldwide, the most common questions asked by patients are whether to start a medication, which one, and for how long... By including studies published up to April, 2017, and previously unpublished information, Cortese and colleagues' results clarify inconsistencies in earlier reviews and meta-analyses, some of which have generated much controversy... Regarding the three common questions patients ask, the extant literature meant that the network meta-analysis could derive only part answers, including general support for short-term medication use, basic guidelines about first-line medications based on age, and little to no data for duration of treatment. These results—and particularly limitations of the data obtained—call for future research that translates directly to clinical practice."

More information: *The Lancet Psychiatry* (2018). www.thelancet.com/journals/lan ... (18)30269-4/fulltext



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