

Why not try a non-stimulant to treat ADHD?

Dr Mukesh Kripalani (consultant psychiatrist), Dr Muffazal Rawala (consultant psychiatrist).

Corresponding author

M Kripalani, Consultant Psychiatrist, ADHD Centre, 85 Wimpole St, Marylebone, W1G 9RJ, UK,

E-mail : drmukesh@doctors.org.uk

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Abstract

It is widely known and believed on the basis of various International guidelines that stimulant medication is considered the cornerstone for treatment of childhood and adult ADHD (attention deficit hyperactivity disorder); there is also now an understanding that it may also be a reason for the perpetuation of stigma of having a condition like ADHD. We would like to raise the profile of non-stimulant medications for ADHD and ensure prescribers have an equitable view on both options of medical interventions and are able to provide their patients with adequate information for both classes for a collaborative informed decision to be made, rather than a homogenous stimulant based treatment plan, for a clinically heterogeneous condition like ADHD.

ADHD is a highly heritable condition and has attracted a great deal of attention lately and the number of prescriptions being issued for this condition have increased significantly over the last 10 years. Most guidelines recommend stimulants such as Elvanse (Vyvanse: Lisdexamfetamine), Adderall or Methylphenidate (preparations like Medikinet xl, Concerta xl etc) as first line treatments, due to higher efficacy rates and to avoid delay in response to treatment, as these medications are fast acting and improvements in ADHD symptoms are immediately evident (1).

Given the above, many clinicians and their clients frequently do not consider the use of non-stimulant medications, even when a non-stimulant may be more appropriate (non-stimulant medications include atomoxetine, guanfacine, bupropion, clonidine and recently available viloxazine).

Stimulant medications have historical precedence over non-

stimulants and have been used to treat ADHD since at least the 1960's. The non-stimulants medications have only been in use since the early 2000's, for example in the UK, non-stimulant medication Atomoxetine, obtained a licence for treatment in ADHD in 2002.

Despite medication interventions for ADHD having the potential to be life changing, the use of ADHD medications, especially in children, continues to attract a great amount of stigma in families, the press, and amongst the general public and within members of the medical community.

One of the main reasons for this stigma is the use of stimulant medications, which include concerns about growing tolerance to medication, dependence, paradoxical decompensation and the risk of stimulant abuse (2). These are the most commonly expressed fears and hence pose the potential of non-compliance to the treatment plan or avoidance of identification of ADHD, especially by caregivers of children, and hence seeking an alternative narrative for their child's behaviour. We now know that this perceived stigma is itself a recognised risk factor for negative outcomes for ADHD (3). It can contribute to the development of co-morbid psychiatric conditions and is also likely to contribute to the increased risk of suicide, among other negative outcomes (4).

Why do we not consider non-stimulants as the first line?

The 2014 Japanese clinical guidelines for treatment of ADHD, recommends both stimulants and non-stimulants as first-line pharmacological treatment for children and adolescents (≥ 6 years) with ADHD. The European and North American guidelines recommend stimulants as first-line pharmacological treatment, followed by non-stimulants, such as Atomoxetine or Guanfacine extended-release (GXR), for those who do not respond to or cannot tolerate stimulants (5). If the European and North American guidelines were to put stimulant and non-stimulant medication on a similar footing, as in the Japanese guidance, that could overcome the reticence of some clients and parents about the stigma of using medication for ADHD. It could allow an open dialogue where the caregivers' and patient's concerns are validated, and could be resolved with an effective alternative plan, in the best interest of the individual affected by the impairments and challenges of having ADHD.

In this article, we would like to look at and debate the arguments for and against the usage of stimulant as compared to non-stimulant medications for the treatment of ADHD.

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Advantages of stimulant medications.

Stimulant medications work immediately and the improvements in symptom control are considered to be superior to what can be achieved by non-stimulants. When comparing the efficacy of medications for ADHD in children, adolescents, and adults, a systematic review and network meta-analysis by Samuele Cortese et al published in 2018 (6) make essential reading. It demonstrated that when core symptoms of ADHD are treated (symptoms rated by clinicians), in children and adolescents closest to 12 weeks (in contrast to placebo), the SMD (standardised mean difference) in improvements was -1.02 , (95% CI -1.19 to -0.85) for amphetamines, and -0.78 , (-0.93 to -0.62) for methylphenidate. In adults (clinicians' ratings), the improvement for amphetamines were SMD -0.79 , (95% CI -0.99 to -0.58), and for methylphenidate -0.49 , (-0.64 to -0.35).

However, we are aware of burgeoning literature (especially for tolerability) indicating tolerability and efficacy depends on an individual's DNA make up to a large extent (<https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling>) amongst other variables.

In some patients, the withdrawal of stimulant medication (usually experienced daily) can have a positive impact as some individuals prefer to go back to their old unmedicated selves (higher ability to enjoy things in life and thrill seek a bit more, and those in the creative fields anecdotally talking about 'the special spark of ADHD being numbed'), but there are risks to this as included below.

Disadvantages of stimulant medication.

It is well known that the stimulant medication does wear off daily (withdrawal impact: statistically significant increase in both hyperactive and defiant behaviour) on a daily basis (7). This has been linked to higher rates of accidents among other consequences as the patient is usually worse than baseline (8).

Stimulants are governed by controlled drug laws as there is a risk of dependence and diversion (hence restricted to 4 weekly prescriptions and specific international requirements need to be satisfied when travelling). The side effects could be quite prominent, and the overall impact of stigmatisation is a concern.

In the above Samuele Cortese meta analysis (6), with respect to tolerability, amphetamines were inferior to placebo in both children and adolescents (odds ratio [OR] 2.30 , 95% CI 1.36 – 3.89) and adults (3.26 , 1.54 – 6.92). Methylphenidate (2.39 , 1.40 – 4.08), and modafinil (4.01 , 1.42 – 11.33) were less

well tolerated than placebo in adults only.

Stimulant medications are often contraindicated in patients with co-morbid disorders, including Tourette's syndrome and bipolar disorder, as well as in patients at risk for substance abuse (9). Further, some investigators advise caution in prescribing these products to patients with co-morbid disorders that are not explicitly contraindicated, such as non ADHD related anxiety disorders, as the latter could be exacerbated.

In a concerning article from Karen Curtin and colleagues (10), it has been suggested that there could be a link between psychostimulant medication and Parkinson's disease. In about 4960 ADHD patients prescribed psychostimulants, risk of basal ganglia and cerebellum diseases between ages 21 and 49 years was especially pronounced, as 8.6-fold (95% CI: 4.8 – 15.6 ; $P < 0.001$). However, any causal link is yet to be proven.

For a full list of side effects of stimulant medication, please also look at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3012210/>.

Disadvantages of non-stimulant medication.

Traditionally, non-stimulants are slower to take effect and it can take as long as 12 weeks before the evidence of improvements in ADHD symptoms could be gauged from a functioning perspective. However, the improvements could often be evident by the end of the first week of use in some individuals.

Non-stimulants might not be well tolerated but it can also be viewed from a genetic perspective. Flattening of mood and a risk of suicidal thoughts are mentioned (0.4%) though the flattening of mood was not found to be the case in a study by M Davies et al (11, 12).

In Samuele Cortese (6) meta analysis above, atomoxetine (2.33 , 1.28 – 4.25) was less well tolerated than placebo in adults only.

For a full list of side effects of non-stimulant medication, please also look at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3012210/>.

Advantages of non-stimulant medications

The symptoms of ADHD are permanent traits, which can cause dysfunction throughout the day and night-time. Compared to stimulants which are designed for fast onset and wear off, the non-stimulants medications usually have a lasting impact which are usually longer than the 24 hours. This level of consistent symptom control is often more effective for long-term executive functioning management and also avoids the common side-effect of withdrawal symptoms associated with

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stimulant medications. Even with several missed doses, patients taking non-stimulants do not tend to encounter significant withdrawal symptoms (12,13,15).

Moreover, as non-stimulants do not produce the same spikes in dopamine release as stimulant medication, they have a negligible potential for abuse. Consequently, atomoxetine is considered a first-line therapy for patients at risk for substance abuse disorders.

Another advantage of the lack of withdrawal effects, atomoxetine can also be stopped without the need for tapering of dose and this can be a significant advantage when considering changing medication (12,13,15).

In other patients with ADHD and other co-morbid conditions such as tic disorders or anxiety disorders, atomoxetine is often better tolerated and do not aggravate the co-morbid condition, as compared to stimulants (13).

In patients with ADHD and co-morbid Parkinson's disease, atomoxetine has been shown to improve several markers of executive dysfunction including impulsivity, risk taking, and global cognition (14).

Data from recent longer-term studies that incorporate current ADHD trial design concepts also show that there is equivalent efficacy for atomoxetine and methylphenidate, both in adults and children (9). A network meta-analysis of atomoxetine and osmotic release oral system methylphenidate in the treatment of attention-deficit/hyperactivity disorder in adult patients suggested that the efficacy of atomoxetine and OROS methylphenidate in adults does not differ significantly (16). A systematic review of atomoxetine data in childhood and adolescent in attention-deficit hyperactivity disorder, suggested atomoxetine may demonstrate similar efficacy to methylphenidate when comparing reduction in core ADHD symptoms in meta-analysis, although the diversity of the data makes interpretation complex. From epidemiological databases, cardiovascular and suicide-related events were similar to those seen in patients taking methylphenidate (17).

A clinically heterogenous condition like ADHD deserves a more individualised clinical approach – our views, experience and commentary:

The current UK NICE guidelines for treatment of adult ADHD (<https://www.nice.org.uk/guidance/ng87/chapter/recommendations#medication-choice-adults>) advises to "Offer atomoxetine (the only licensed non-stimulant medicine option for treatment of adult ADHD patients in UK) to adults if: they cannot tolerate lisdexamfetamine or methylphenidate or their symptoms have not responded to separate 6-week trials of lisdexamfetamine and methylphenidate, having

considered alternative preparations and adequate doses."

In children and adolescents, the NICE guidelines advise

"Offer atomoxetine or guanfacine to children aged 5 years and over and young people if: they cannot tolerate methylphenidate or lisdexamfetamine or their symptoms have not responded to separate 6-week trials of lisdexamfetamine and methylphenidate, having considered alternative preparations and adequate doses."

We feel that this unfortunately leads to an unnecessary clinical restriction of treatment for a heterogenous condition like ADHD. The popularity of stimulant medications for ADHD has been established both on research evidence as well as their clinical use since 1960. Our aim is not to challenge the efficacy of stimulant medications, which we accept are quite effective. We feel that a greater availability of options in terms of non-stimulants for patients to make an informed, flexible and collaborative decision, for their individual functional impairments due to ADHD, may lead to a more individualised treatment plan, to manage the wide variety of clinical presentations (co-morbidity). We believe in a collaborative approach with the patient, keeping clinical acumen, individual circumstances and evidence bases in mind. One should have the option of choosing either a stimulant or non-stimulant medication that would help with patient satisfaction, compliance and a greater acceptance of their medication and treatment.

As a clinician, one is always aware that stimulant medications are controlled substances and could carry a potential risk of addiction and abuse. For parents of children with ADHD, in spite of comprehensive psycho education sessions, the potential risk of addictions, abuse and other potential side effects like tics, weight loss, anxiety and sleep problems can lead to refusal of ADHD medications. This decision could have a significant effect on the child's well-being with its effects lasting into adulthood. In such situations, one must query, and we have debated this with our clinical peers, if the advice around the consideration of non-stimulants as second line option to stimulant medications is too narrow, restrictive and simplistic.

Moreover, why would a 24/7 condition not deserve a 24/7 response?

Does the patient not present with ADHD symptoms when the stimulant medication wears off? If patients are doing shift work, should we just restrict medication prescribing to the shifts they work? Should we not explain the increased risk of encountering an accident when the medication wears off due to withdrawal symptoms or the presence of stimulant crash leading to significant increase in impulsivity in some

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individuals. Do we not have a duty to ensure a full and open discussion which includes the option of a non-stimulant medication?

In our clinical work, we tend to use the approach of individualised treatment, when we look to improve the impairments associated with ADHD.

No two individuals with ADHD have the same struggles, the same challenges or the same medical problems, social issues, risks of addictions etc; and the choice of medication should be made in a pragmatic manner with the pros and cons of stimulant and non-stimulants are discussed, when formulating a management plan. This of course needs to be backed up with a comprehensive psycho-social management plan.

In short, the 'one size fits all' approach to the medication management of ADHD has become outdated. Given our growing understanding of the heterogeneous clinical presentations of ADHD, our patients deserve a more nuanced and considered approach to their symptom management. We will leave it to the readers discretion, as it certainly appears to be a critical juncture in the developments of more sophisticated treatments for ADHD.

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