Review Article

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Drug Therapy of Attention Deficit Hyperactivity Disorder: Current Trends

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ABSTRACT

Attention deficit hyperactivity disorder is a developmental disorder with an age onset prior to 7 years. Children with ADHD have significantly lower ability to focus and sustain attention and also score higher on impulsivity and hyperactivity. Stimulants, such as methylphenidate, have remained the mainstay of ADHD treatment for decades with evidence supporting their use. However, recent years have seen emergence of newer drugs and drug delivery systems, like osmotic release oral systems and transdermal patches, to mention a few. The use of nonstimulant drugs like atomoxetine and various other drugs, such as α-agonists, and a few antidepressants, being used in an off-label manner, have added to the pharmacotherapy of ADHD. This review discusses current trends in drug therapy of ADHD and highlights the promise pharmacogenomics may hold in the future.

Key Words: *ADHD; α-agonists; Antidepressants; Atomoxetine; Attention deficit hyperactivity disorder; Bupropion; Children; Clonidine; Dopamine; Drug delivery systems; Guanfacine; Lisdexamphetamine (LDX); Methylphenidate; Mixed Amphetamine Salts; Modafinil; Non-stimulants; Pemoline; Pharmacogenomics; Preschool ADHD; Reboxetine; Selegiline; Stimulants; Theophylline; Venlafaxine*

Introduction

Attention deficit hyperactivity disorder (ADHD) is a common psychiatric problem in children. It presents as inattentiveness, over-activity, impulsivity,

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or a combination of these and affects 3-10% of school-going children worldwide (Biederman and Faraone, 2004[13]; Shastri *et al.*, 2010[105]). The disorder is unique in showing marked variability over time, in different situations (for example at school, home and at the clinician's consultation), and within the same child and in similar situations. With an increase in the prevalence of ADHD, there has also been an increase in research based on pharmacotherapy of ADHD.

Pharmacotherapy remains the cornerstone for the management of ADHD, and there have been some recent advances in this area (Prince, 2006[93]; Boyle *et al.*, 2011[18]; Sitholey *et al.*, 2011[106]). First, there has been the development and availability of novel drug delivery systems for methylphenidate (MPH) and mixed amphetamine salts (MAS) that has made it possible to extend full day coverage with a single dose. Second, the emergence of atomoxetine (ATX), a noradrenergic medication, has allowed us access to alternate neurotransmitter systems in children where stimulants fail. These two, coupled with development in the pharmacogenomics of ADHD, are set to usher in various newer trends in its drug management.

This review article discusses various drugs used in ADHD management starting with older drugs like stimulants, moving on to ATX, and finally looking at off-label drugs. It deals mainly with current trends in ADHD Management. To our knowledge, we could not find any relevant Indian literature in this area, which underscores the need for future work in this field in the country.

Stimulants

Stimulants, such as MPH and MAS, are the most widely used medications approved by the US-FDA for the treatment of ADHD in children (Findling, 2008[38]). These medications have a paradoxical effect on individuals with ADHD, calming them and improving both the cognitive (inattention and impulsivity) and the non-cognitive (hyperactivity) domains of the disorder (Swanson *et al*., 2011[121]). All stimulants work by increasing the levels of dopamine in the brain, dopamine being associated with attention, pleasure and movement. When started at lower doses followed by gradual up-titration, stimulants are able to increase dopamine slowly and steadily, producing an effect similar to the natural production of dopamine in the brain. However, when taken in higher doses, or if the dose is increased in a shorter time, stimulants can increase brain dopamine rapidly, producing euphoria and an increased risk of abuse and dependence. Even though stimulants remain the US-FDA-approved medical treatment of choice for ADHD and are associated with an exceptional response rate (Wigal, 2009[131]), around 10-30% of all children and adults with ADHD either do not respond to, or do not tolerate treatment with stimulants (Banaschewski *et al*., 2004[5]).

Methylphenidate

MPH is a psychostimulant drug approved for ADHD. It increases norepinephrine and dopamine levels by inhibiting their reuptake and facilitating their release especially in the dorsolateral prefrontal cortex that improves attention, concentration, executive function and maintains wakefulness. Enhancement of dopamine actions in basal ganglia may explain the improvement seen in hyperactivity symptom of ADHD with MPH. This amplifying effect of MPH on release of dopamine improves attention and focus in individuals who have weak dopamine signals (Volkow *et al*., 2002[125]). MPH improves overall productivity and accuracy on arithmetic assignments, reduces disruptive behavior, and improves classroom rule-following and negative behavior in the child (Pelham *et al*., 2001[83]).

Expert consensus recommends MPH as the first line medication to be used in a treatment algorithm for ADHD in children and adolescents (Greenhill *et al*., 2002a[44]; Wolraich *et al*., 2010[139]). In case of no response or partial response, optimising the doses, or switching to other agents is the recommended step. It is also worth addressing and assessing non-compliance issues and any co-morbid conditions. There are various preparations of MPH available and various delivery forms to facilitate dosages in a once-a-day format.

Case Vignette: *A 7-year-old female child was referred for poor concentration and reduced 'interest' in classes while the teacher was teaching. She would make careless mistakes while writing dictation, often coming home with incomplete notes. She would lose her things in school daily and would have difficulty sitting in one place for a long time with a lot of fidgetiness. She was also known to be hyperactive. The teachers would complain about her distractibility to the smallest of stimuli during teaching hours in class. Her IQ on Wechsler Intelligence Scale for Children was 115 and there were no other significant problems in her psychosocial history. Her father had a history of similar problems.*

Discussion: *This child with ADHD is a suitable candidate for MPH. Clinical experience shows that ADHD primarily of inattentive type responds better to MPH.*

MPH – immediate release (MPH-IR)

Immediate release MPH (MPH-IR) has a short half-life of approximately 2 to 3 hours (Swanson *et al*., 1978[118]; Greenhill, 1992[43]; Atzori *et al*., 2009[4]). This requires multiple daily doses that pose problems for dosing during school timings and can thus compromise patient compliance. It also compromises confidentiality issues as the patient is required to take the medication during school hours (among other classmates), who may not be able to understand the patient's condition, further stigmatising his/her experience with the illness. The dose range for MPH-IR is 0.3-1mg/kg TID up to a maximum of 60 mg per day (Atzori *et al*., 2009[4]).

MPH – extended release (MPH-ER)

MPH extended release formulation provides the benefit of a lasting effect that is maintained even about 12 hours after dosing and is equivalent to twice- or thrice-daily dosing of plain MPH. Studies support the use of MPH-ER formulation that provides benefits throughout the day and early part of the evening (Pelham *et al*., 2001[83]; Mikami *et al*., 2009[73]). Some newer ER formulations produce therapeutic effects by the MPH dose being delivered initially by a bolus that achieves peak plasma concentrations in early morning within 2 hours of dosing, and a second extended and controlled delivery of the drug that achieves the required plasma concentrations in the afternoon (Swanson *et al*., 2002[119], 2003[120]; Mikami *et al*., 2009[73]). Thus, with the ER formulations, one achieves effective symptom control throughout the day. The dose range for MPH-ER is the same as for immediate release formulation, except that it has to be dosed once in the morning. [The IR- and ER- preparations are the more commonly and easily available formulations in different parts of the world, including India; however those mentioned hereafter are not yet universally available].

Newer Drug Delivery systems for MPH

MPH – osmotic release oral system (MPH-OROS)

This is a preparation of MPH with a novel drug delivery system using the osmotic pump process as a release mechanism. It was launched in the US in August 2000 and is not yet available in India. It consists of a 50:50 racemic mixture of D, l-threo MPH. It has a 12-hour coverage period per dose and, the release system being gradual, prevents any form of tachyphylaxis. It is available as an 18mg caplet, where 4mg is released as a bolus and additional delivery is in the form of an ascending profile similar to MPH-IR being given at a dose of 5mg thrice a day (Swanson *et al.,* 2003[120]).

There have been some important randomised controlled trials using OROS-MPH with interesting findings. Though different dosages have been tried, it has been noted that the effect sizes with both MPH-IR and OROS-MPH have been the same (Wolraich *et al.,* 2001[138]). Side effects have been mild in the form of headache, drowsiness and irritability (Pelham *et al.,* 2001[83]). It has been noted that lower doses of OROS-MPH are needed in children with ADHD inattentive type compared to children with a combined type of ADHD (Stein *et al.,* 2003[115]). There have been long-term studies for periods in the range of 8-24 months with OROS-MPH indicating good efficacy and tolerability (Wilens *et al.,* 2003a[133]; Steele *et al.,* 2004[114]).

MPH – modified release (MPH – MR)

This is a form of MPH that uses a release system made up of two types of coated beads consisting of MPH-IR and MPH-ER in a 30:70 ratio. It is available in 20mg capsules with 6mg of MPH-IR and 14mg of MPH-ER. The 1st peak in dosage is in 1.5 hours with MPH-IR and the second peak in dosage is in 4.5 hours with MPH-ER. The beads can be sprinkled on food or mixed in a drink. The capsule has been designed to simulate a twice a day MPH-IR dosage. Further studies are warranted to gauge the efficacy and usage of this preparation (Greenhill *et al.,* 2002b[45]; Faraone and Buitelaar, 2010[36]).

Methylphenidate-extended release capsules (ERC)

This is a preparation of MPH that uses the spheroidal oral drug absorption system (SODAS). It is available as 10, 20, 30 and 40 mg capsules. It has bimodal release profile with 50% of the drug i.e. d,l-threo MPH releasing initially and the other 50% releasing after 3-5 hours. It thus provides 8-hour coverage. The side effect profile is mild too. A study has shown an effect size of 0.9 with this treatment and no major adverse effects (Biederman *et al.,* 2003a[11]).

D-threo-methylphenidate, D – methylphenidate (D-MPH)

As originally formulated, MPH was produced as an equal mixture of D,l-threo-MPH and D,l-erythro-MPH. It was later recognised that the erythro form of MPH was responsible for the cardiovascular side effects of MPH, and thus MPH has been manufactured as an equal mixture of D and L-threo MPH. Studies have revealed that the D form is the primary active form of MPH (Ding *et al.,* 1997[31], 2004[32]). Thus the D form is now available as tablets of 2.5, 5 and 10 mg. It is worth mentioning that 5 mg D-MPH is equivalent to 10 mg MPH-IR. The drug has been studied and is well tolerated in open trials and controlled studies with minimal side effects (Silva *et al.,* 2004[107]; Wigal *et al.,* 2004[129]). Using the SODAS beaded technique there is an extended release preparation of D-MPH available in 5, 10 and 20 mg capsules (Greenhill *et al.,* 2006[47]).

MPH transdermal patch

MPH has been investigated for use as a transdermal patch in sizes of 6.25cm^2 (0.45mg/hour), 12.5cm^2 (0.9mg/hour) and 25cm^2 (1.8mg/hour). The only side effects noted in the study conducted were erythema at the site of the patch, mild insomnia in a few subjects, and decreased appetite (Pelham *et al.,* 2005[84]). Such innovative yet investigational methods of drug delivery may pave the way for easy drug administration in a regular manner throughout the day in children with ADHD.

Amphetamine and Related Drugs

Mixed amphetamine salts

In recent years, both immediate and extended release preparations of MAS have been studied in clinical trials. MAS tablets contain equal proportions of D-amphetamine saccharate, D,l-amphetamine asparate, D-amphetamine sulfate and D,l-amphetamine sulfate. The two isomers have different properties and some children may respond better to one isomer than the other. The peak behavioral effects of MAS occur later than MPH-IR and are more sustained. It has also been noted in studies that a twice-daily dosage is superior to a once-daily dosage (Plizska *et al.,* 2000[87]; Greenhill *et al.,* 2003[46]; Hechtman, 2011[53]).

MAS – extended release (MAS-ER)

The MAS-ER preparation contains a 50:50 ratio of immediate release beads designed to release MAS in a fashion similar to MAS tablets and delayed release beads designed to release MAS 4 to 6 hours after the dosing. Clinical trials in both large and small groups of prepubertal children have shown that response and effect size is good with stimulant naïve subjects, who respond equally well as compared to children who have been treated previously with stimulants. Long-term studies over 24 months have reported that MAS-ER has been well tolerated and resulted in significant and sustained clinical benefits (Biederman *et al.,* 2002[10]; McGough *et al.,* 2005[69]).

Pemoline

Pemoline is a central nervous system stimulant structurally different from amphetamine and MPH, and acts via enhancing central dopaminergic transmission. Since its availability in 1975, 15 cases of acute fulminant hepatic failure with pemoline have been reported. US-FDA recommends liver function tests every 2 weeks while on the drug. Hence the use of pemoline has been relegated to only rare circumstances (Sallee *et al*., 1992[100]; Patrick and Markowitz, 1997[82]; Safer *et al*., 2001[99]).

Lisdexamphetamine (LDX)

A recently approved prodrug stimulant, LDX converts to dextroamphetamine in the blood stream due to the action of a peptidase enzyme and provides a longer duration of effect that is consistent throughout the day (Findling, 2008[38]). As a prodrug it does not become active until after it is metabolized. This lowers its ability to be diverted and abused in an intranasal or intravenous manner. It is available in capsule form that can be dissolved in water when the patient may not be able to swallow. Its longer duration of action provides 12-hour coverage with a single dose (Biederman *et al.,* 2007a[14]). Patients on LDX may complain of typical

amphetamine side effects such as decreased appetite, nausea, weight loss, upper abdominal pain, insomnia, headache and irritability (Najib, 2009[77]). Studies suggest that LDX may form an integral part of a total treatment programme for ADHD in the future. Clinical evidence supports its efficacy and tolerability in the management of ADHD (Najib, 2009[77]). At equivalent doses, LDX had lower abuse potential compared with immediate release d-amphetamine (Findling, 2008[38]; Najib, 2009[77]). The recommended starting dosage is 30 mg orally daily that can be adjusted to a maximum dosage of 70 mg/day (Popovic *et al*., 2009[89]).

Side effects with stimulant drugs

Knowing the side effect profile of these drugs is important since side effects could be a major reason for non-adherence to treatment (Sitholey *et al*., 2011[106]). The various MPH formulations (IR and ER) are reported to have similar effect and side effect profile (Pelham *et al*., 2001[83]; Stiefel and Besag, 2010[117]). Various side effects of MPH include insomnia, headache, nervousness, irritability and dizziness. MPH may have gastrointestinal side effects like anorexia, nausea and abdominal pain. It is also reported to reduce seizure threshold in some patients, thus precipitating seizures. Although new onset seizures and drug-drug interactions between MPH and antiepileptic drugs (AEDs) have been reported, open-label trials suggest otherwise, with no effect of MPH on either seizure or AED serum levels (Baptista-Neto *et al*., 2008[8]). A worsening of tics with stimulants may be seen in some but not all patients, although this is a major limiting factor in their use in such patients (Pringsheim and Steeves, 2011[94]).

Treatment of ADHD comorbid with tic disorders cannot be ignored given the impact that ADHD has on these patients, and MPH appears to be the best-tolerated stimulant compound in such patients (Kurlan, 2003[63]). Although use of stimulants has been avoided in patients with autism spectrum disorders (ASD) due to the concern that they worsen stereotypies, studies suggest otherwise (Santosh *et al*., 2006[103]): autistic patients with ADHD show significant improvements in the symptom clusters of ADHD along with aggression and oppositionality seen in autism (Santosh *et al*., 2006[103]). MPH is also known to cause pupil dilation leading to blurring of vision (Jaanus, 1992[55]). Complex visual hallucinations have been reported with MPH (Halevy and Shuper, 2009[50]). There is some amount of risk of abuse with MPH-IR formulations (Findling, 2008[38]). Concerns on an increase in the risk of drug and alcohol abuse disorders later in life in ADHD children treated with stimulants have not been supported by research (Wilens *et al*., 2003b[134]; Biederman *et al*., 2008a[16]; Mannuzza *et al*., 2008[66]).

An emerging area of concern has been the effect of stimulant drugs on cardiovascular function. It is well known that these medications have an effect on heart rate (HR), systolic and diastolic blood pressure (SBP and DBP). On an average, patients on stimulant drugs reported that while on the medication in optimal doses, there is an increase in HR by 1-2 beats per minute, and SBP

and DBP by 3-4 mmHg (Findling *et al*., 2001[37]). This increase is linear with increase in dosage. Although statistically significant there has been no clinical event as a result of these changes in cardiovascular parameters. It is, however, advised that an electrocardiogram (ECG) be done in every child before starting on stimulants, and this may be supplemented by a 2D echocardiography (2D ECHO) when needed (Findling *et al*., 2001[37]). Recent studies have reported statistically significant yet clinically minor changes in HR, SBP and DBP even with OROS-MPH and MAS-ER preparations (McBurnett and Starr, 2011[70]). There have been reports of sudden cardiac deaths with MPH and MAS, but in all cases, post mortem examination revealed a structural heart defect that was not investigated prior to starting medication (Wilens *et al.,* 2004[135]).

Sleep disturbances are common in children with ADHD. The increased prevalence of sleep disturbances in ADHD has not been correlated to stimulant drugs that have been shown to have little detrimental effect on sleep characteristics (Cohen-Zion and Ancoli-Israel, 2004[23]). Melatonin and small doses of Clonidine have been advocated for the treatment of sleep problems in ADHD (Prince *et al.,* 1996[92]; Tjon Pian Gi *et al.,* 2003[122]). Patients treated with stimulants experience dose-related reduction in appetite and in some cases, weight loss (Rapport and Moffit, 2002[96]). Cyproheptadine, an antihistaminergic and antiserotonergic medication, has been suggested as useful for stimulant induced appetite suppression. Nutritional options with higher caloric diet may be another option (Daviss and Scott, 2004[29]). Coupled with appetite suppression, concern surrounds the impact of stimulant therapy on the rate and extent of growth in children (Biederman *et al.,* 2003b[12]). The current consensus is that stimulants may infrequently produce a small negative impact on growth velocity; however, this delay may be related more to ADHD than to its treatment. The role of drug holidays or temporary periods of medication discontinuation to minimise the growth effect has not been supported by research data, though clinically this method may be more practical (MTA Cooperative Group, 2004[78]). It is worth noting that MPH has not been approved for use in children below six years of age (Vitiello, 2001[124]; Hermens *et al*., 2006[54]). Predictors of poor clinical response to MPH include ADHD combined type, comorbid oppositional defiant disorder and maternal ADHD symptoms (Chazan *et al*., 2011[21]).

Non Stimulants

Atomoxetine

ATX is the first non-stimulant treatment approved by the US FDA and is an effective alternative to stimulants, especially for patients who have comorbidities that contraindicate their use. It is also the first ADHD treatment to be approved for use in adults with ADHD (Simpson and Plosker, 2004[108]; Hammerness *et al.,* 2009a[51]). ATX has a negligible risk of abuse and is therefore considered

particularly useful for patients who may be at such risk. Patients with comorbid anxiety or tics, and oppositional symptoms, or those who do not wish to take a controlled substance may be given a trial of ATX. Dosing with ATX involves weight-based dosing up to 1.4 mg/kg/day; benefit is generally observed within 2-8 weeks of initiation of treatment (May and Kratochvil, 2010[68]). In the case of ADHD, practice parameters from the American Academy of Child and Adolescent Psychiatry provide clear guidelines and describe the three common approaches taken by clinicians in dose titration with ATX: prescribing and waiting for the effects to occur, gradual up-titration of the dose until behavioral improvement is seen, and increasing the dose until side effects occur with gradual reduction of the dose to the level before the side effects appeared (Greenhill *et al*., 2002b[45]; Manos *et al*., 2007[65]; Daughton and Kratochvil 2009[27]). It has been suggested that treatment algorithms involving the initial use of atomoxetine appear more cost-effective as compared to algorithms involving initial use of MPH or other medications (Garnock-Jones and Keating, 2009[40]).

Pivotal studies documenting the efficacy of ATX in ADHD started in 2001 (Spencer *et al*., 2001[110]). Results from large randomised controlled trials have shown that teachers and parents report similar improvements in their children when ATX is used over long periods (Weiss *et al*., 2005[127]). A recent meta-analysis has reported good efficacy and safety of ATX in children with ADHD (Cheng *et al*., 2007[20]). However, when studies on ADHD are reviewed, it is worth noting that superior effect sizes compared to ATX have always been consistently noted with MPH-IR and MPH-ER (Faraone *et al*., 2006[35]). In short term studies of 4-8 weeks, a greater improvement has been noted with MPH and MAS compared to ATX (Wigal *et al*., 2005[130]), while in long term studies over a period 10-14 weeks or more, ATX is as efficacious as MPH (Kratochvil *et al*., 2006[60]).

Theoretically, twice-a-day dosage of ATX appears better than a single dosage, but most studies document improvement with a once daily dosage alone (Michelson *et al*., 2002[72]; Kelsey *et al*., 2004[58]). Newcorn *et al*., 2008[80], demonstrated that ATX elicits a lower response from children who have received stimulants prior to starting ATX compared to children who are stimulant naïve. The mechanism for this is not yet understood but this has not been the case in other studies where ATX has shown an equivalent response in both the above groups (Quintana *et al*., 2007[95]; Hammerness *et al*., 2009b[52]). ATX has also been reported to be effective when combined with stimulants, though side effects like insomnia and reduced appetite increase with this combination (Carlson *et al*., 2007[19]). In case it is needed, shifting a patient from MPH to ATX requires gradual cross-titration and poses no major problem (Quintana *et al*., 2007[95]). ATX has also shown good efficacy in long-term studies over 2 years and 5 years with all effects sustained and well maintained (Kratochvil *et al*., 2006[60]; Spencer *et al*., 2007[111]). In other studies, when ATX has been used in children with ADHD and oppositional defiant disorder, it has been noted that larger doses of ATX were needed to reduce hyperactivity symptoms, but there was little change noted in

oppositional behavior (Biederman *et al.,* 2007b[15]; Bangs *et al.,* 2008[7]). ATX has also been demonstrated, in small studies, to have a positive effect on anxiety and depressive symptoms that may accompany ADHD, unlike MPH (Geller *et al.,* 2007[41]; Bangs *et al.,* 2007[6]).

Side effects with atomoxetine

The side effect profile of ATX is milder than that of stimulants. Common side effects include decreased appetite and weight, irritability, sedation or insomnia, dizziness, abdominal pain and fatigue. While patients may complain of an initial loss in expected height and weight, this may eventually return to normal in the long term (Garnock-Jones and Keating, 2009[40]); hence reassuring concerned parents about this is important. Although considered safer, there have been rare case reports of exacerbation (Parraga *et al*., 2007[81]) or development (Sears and Patel, 2008[104]; Ledbetter, 2005[64]) of tics with ATX. It is important to keep a watch for suicidal ideations in patients on atomoxetine (Polzer *et al.,* 2007[88]) though such episodes may be rare. At routinely prescribed doses and as seen in various trials there is no significant effect of ATX on the cardiovascular system in children as well as no reports of sudden cardiac death (Perrin *et al*., 2008[86]). There are rare reports of seizures with ATX and the percentage has been 0.1-0.2% (Wernicke *et al.,* 2007[128]). No deaths have been reported when poison centre reports were analysed for ATX overdoses, and doses up to 2840 mg have been reported to cause seizures and GI problems (Kashani and Ruha, 2007[56]; Spiller *et al*., 2005[113]). In a double-blind study in 6- to 16-year-old outpatients with ADHD from three different countries, Wang *et al.,* 2007[126], reported a higher incidence of adverse effects with ATX compared to MPH.

Case Vignette: *Parents brought a 9-year-old boy with a history of deteriorating grades in school and poor peer relations. The parents were receiving frequent complaints from school regarding his inattention and increasingly mischievous behavior during class, which led to punishments. This problematic behavior did not improve despite changing his sitting position. He was a known case of seizure disorder since past 3 years and was on regular medications with no seizures in the past 2 years. His father was a known case of alcohol dependence with multiple failed attempts at abstinence and was presently not on any treatment.*

Discussion: *The drug of choice in this child would preferably be* ATX. *Two risk factors in this child's history push the decision in favor of ATX: history of seizures in him, and of substance use in his family.*

Non US FDA approved Medication used in ADHD

While stimulants are clearly the most effective agents, other drugs may also be useful. Additional therapy with non-stimulants (other than ATX) is warranted

if the patient fails to respond to trials of two different stimulants, has intolerable side effects with stimulants, or fails to respond to ATX (Manos *et al*., 2007[65]).

Clonidine and guanfacine

Alpha-adrenergic agonists have been recommended in patients with a suboptimal response to psychostimulants, or in whom they cannot be tried (Sallee, 2010[102]). Both these drugs are available in India. Studies have shown that guanfacine extended release can be safely administered with MPH or amphetamine and gives good clinical results in ADHD (Spencer *et al*., 2009[112]). The rationale for combining α-adrenergic agonists with stimulants is the complementary mechanisms of action of the two classes of drugs involving different neurotransmitter systems that together modulate prefrontal cortex functioning (Sallee, 2010[102]). Various adverse effects include headache, fatigue, sedation and cardiovascular adverse events. One has to be vigilant and monitor changes in blood pressure and heart-rate during treatment with guanfacine; it is also better to avoid this drug in children with cardiovascular pathology (Connor and Rubin, 2010[25]).

Immediate release clonidine and guanfacine have limited use as they are rapidly absorbed and cleared from the body and have negative side effects. However, the newer controlled-release formulations of these two drugs have overcome these limitations and have proven effective in ADHD. A selective alpha (2A) adrenoceptor agonist, guanfacine extended-release is a once a day formulation that significantly improves the symptoms of inattention and hyperactivity-impulsivity in a dose range of 1-4 mg/day. Its efficacy has been demonstrated in both short-term and long-term studies (Biederman *et al*., 2008b[17]; Sallee *et al*., 2009[101]).

Bupropion

Bupropion has been used in certain cases of ADHD but has been associated with the onset or exacerbation of tics in these children (Ledbetter, 2005[64]). It is found to be useful in some cases of ADHD coupled with nicotine dependence because of its primary effect on smoking cessation (Upadhyaya *et al*., 2004[123]). It has also been useful to lift depressive symptoms that may accompany ADHD (Daviss *et al.,* 2001[28]). Its efficacy is lesser than that of stimulants or ATX. Irritability and tics are commonly noted side effects. It is available as immediate release, extended release and sustained release preparations (Wilens *et al.,* 2005[136]; Daviss *et al.,* 2005[30]).

Modafinil

A novel stimulant distinct from amphetamine, modafinil has been US FDA approved for the treatment of narcolepsy and is easily available in Indian markets.

It acts by activating specific hypothalamic regions. It has been shown to improve cognitive and meta-cognitive skills in non-sleep deprived adults (Baranski *et al.*, 2004[9]). Published trials in ADHD show mixed results but definitely advocate the case for modafinil as a supplemental medication in the management of ADHD (Biederman *et al.*, 2003b[12]).

Other drugs with anecdotal evidence

Certain studies have shown the benefits of selective norepinephrine reuptake inhibitor drug Reboxetine in the management of ADHD (Cohen-Yahin *et al.*, 2009[22]; Arabgol *et al.*, 2009[3]; Hechtman, 2011[53]). Similar reports exist for Venlafaxine, a drug from the same family (Ratner *et al.*, 2005[97]). Selegiline, another drug, is an irreversible type B monoamine oxidase inhibitor that is metabolised into amphetamine and methampetamine. Certain trials show modest efficacy of this drug in children with ADHD, but potentially life threatening reactions with tyramine rich foods such as cheese, impede the use of selegiline in children who are unlikely to remember or adhere to the dietary restrictions (Akhondzadeh *et al.*, 2003[1]; Mohammadi *et al.*, 2004a[74]). Medications used to slow the decline in Alzheimer's disease have also generated interest in enhancing cognition in the treatment of ADHD.

The effect of cholinergic modulation on attention remains unclear. Studies of these drugs till date remain restricted to case series (Wilens *et al.*, 2000[132]; Narahashi *et al.*, 2004[79]). Based on the high rates of cigarette smoking in adolescents in ADHD and the cognitive enhancing properties of nicotine, transdermal nicotine has been tried in isolated studies to improve the fronto-striatal attention networks in ADHD. At this point though, nicotine is not a viable or recommended treatment, but remains a potential target for the development of novel treatments (Rezvani and Levin, 2001[98]; Potter and Newhouse, 2004[91]). Theophylline, an adenosine receptor antagonist, is a psychostimulant widely used as a bronchodilator. Adenosine antagonism may have an effect on central dopaminergic and noradrenergic neurotransmission and may benefit in conditions like ADHD. Pilot studies support the role of theophylline in paediatric ADHD (Guieu *et al.*, 1996[49]; Mohammadi *et al.*, 2004b[75]). Other agents such as polyunsaturated fatty acids (PUFA), acetyl-L-carnitine, and iron supplements have been shown to improve ADHD symptoms (Dopheide and Pliszka, 2009[33]).

The Treatment of Preschool ADHD

ADHD in pre-schoolers has become established as a valid psychiatric disorder, with prevalence estimates ranging from 2% to 6% in community samples (Keenan and Wakschlag, 2000[57]). Despite some differences in symptom presentation in younger children, similar patterns of comorbidity and impairment have been identified (DuPaul *et al.*, 2001[34]). Many areas of

impairment have been identified among pre-schoolers with ADHD, including relationships with parents, siblings, peers, and teachers, as well as their ability to cooperate with family activities and behave appropriately in public, which requires limitations of activities outside the home (Angold *et al.,* 2000[2]; Murray, 2010[76]). Academically, preschoolers with ADHD perform more poorly on tests of pre-academic skills (Cunningham and Boyle, 2002[26]) and have identified deficits in working memory, planning, and delay of gratification (Sonuga-Barke *et al.,* 2003[109]). Evidence indicates that ADHD may be more severe and complicated in younger children and those with earlier onset ADHD. Within a sample of clinically diagnosed children 3 to 5.5 years of age with ADHD, parents and teachers rated symptoms as more severe in younger children (Posner *et al.,* 2007[90]). Earlier age at onset of ADHD (recalled by parents in annual increments from birth to 6 years of age) within a clinical sample of elementary school-age children was also associated with higher rates of parent-reported aggressive symptoms (Connor *et al.,* 2003[24]). Diagnosis during the preschool years also predicts the development of other psychiatric disorders and creates significant risk for the development of secondary impairments such as school failure and peer difficulties during adolescence.

Prescription guidelines from the US FDA indicate that stimulant medications should not be used in children younger than 6 years of age. However, off-label use has increased dramatically since the 1990s, when 34% of paediatricians and 15% of family practitioners reported prescribing stimulants to pre-schoolers with ADHD (Wolraich *et al.,* 1990[137]; Murray, 2010[76]; March, 2011[67]). Understandably, many concerns have been raised about these practices, including ethical objections to using any medication for children this young, concerns about side effects, and the limited body of efficacy data. Extensive data spanning several decades supports the safety and efficacy of stimulant medication in school-age children; however, few studies have included preschoolers. Prior to the National Institutes of Health– funded PATS, initiated in 2000 (Kollins *et al.,* 2006[59]), there were only 11 publications of 10 controlled stimulant treatment studies, including less than 280 total participants, with many methodological limitations that affected interpretation of outcomes (Greenhill *et al.,* 2008[48]). In particular, most of these studies were not placebo controlled, sample sizes were small, duration of the trials was short, and the diagnostic procedures and side effect reporting were highly variable. The results were mixed, with six reporting good efficacy and safety, two failing to show benefit, and two reporting higher rates of adverse events, including sadness and social withdrawal.

There are only a handful of studies with non-stimulants in preschool-age children with ADHD. One study treated 5 and 6-year-olds with ATX in open-label fashion for 8 weeks in combination with parent education in behavior management adapted from 'Helping the Non Compliant Child' (HNC) provided at each pharmacotherapy visit (Kratochvil *et al.,* 2007[61]). A significant decrease in ADHD symptoms was observed at a dose of 1.25 mg/kg, which is similar to the

dosing for school-age children. Similar to adverse events seen with stimulants, mood lability, decreased appetite and weight loss were common. Results of a recent 8-week, double-blind, placebo-controlled trial of ATX by the same authors in 101, 5 and 6 year olds recruited across two sites show similar findings (Kratochvil *et al.,* 2011[62]). Although 3 and 4-year-olds were not included, and any effects of the psychoeducational component cannot be separated out, this study will greatly increase the existing knowledge base and inform clinicians considering non-stimulant treatment for preschoolers with ADHD (Pelham and Fabiano, 2008[85]).

Despite significant advances made recently in our knowledge of medication use for preschoolers with ADHD, many important questions relevant for clinical practice remain. In particular, stimulant dosing parameters and tolerability issues need further examination, as do the effects of sustained-release formulations in this group. There are literally no data on use of non-stimulants such as ATX in children younger than 5 years. Although there is evidence of benefit of stimulant medication for preschool-age children with ADHD, effects do not seem to be as large, and some of the side effects may be greater than for school-age children, including growth slowing. The long-term impact of medication use for preschoolers beyond 1 year is unclear, although follow-up studies should address this in the near future.

Clinical Aspects of Pharmacogenomics in ADHD

Preliminary evidence suggests that in ADHD, genetic variability plays some role in predicting treatment response (McGough, 2005[71]). The results may differ based on whether teachers or parents are informants. Correlations between various outcome measures, even in the same subjects, are known to be fairly weak, raising the question as to which outcome measure defines the best result. Pharmacogenetic effects are also known to vary amongst ethnic groups. Most published studies in the pharmacogenetics of ADHD examine response to MPH, which is an obvious choice considering the known pathophysiology of DAT1 and its association with ADHD serving as a specific target for stimulant action (Friedel *et al.,* 2007[39]).

Certain prerequisites are essential when conducting pharmacogenetic studies in ADHD (Goldstein, 2003[42]). These are as follows –

1. Pharmacogenetic studies in ADHD should be methodologically rigorous in terms of the pharmacological intervention, which means that the trial should meet criteria for being published on its own.
2. There must be more randomised assignment to treatment or control groups. Response in the trial should always be measured in different ways and at different time points. Functional outcomes, adverse events and symptom ratings must also be evaluated.

3. Different doses of the drug or the optimal dose must be evaluated and dose ranging or forced titration designs are more likely to elicit pharmacogenetic effects than flexible dosing designs.
4. Multiple genes must be examined.
5. Genotyping quality control must be performed by laboratory checks.
6. Samples large enough to look at gene-environment interactions must be studied.
7. Trials sponsored by pharmaceutical companies should routinely collect DNA for pharmacogenetic and subgroup analysis.

ADHD pharmacogenetics may pave the way for development of novel treatments. Gene discovery may promote the discovery of new drug targets. Genotyping may lead to identifying patients who are more likely to show response to a particular drug and thus treatment failures can be minimised. The hope that arises out of this is that ADHD treatments will eventually improve through a more personalised and individualised approach, and personalised ADHD therapy shall soon move from the promise phase to a practical one (Stein and McGough, 2008[116]) [Figure 1].

Concluding Remarks [See also Figure 1: Flowchart of Paper]

Overall, pharmacotherapy of ADHD in children is proven to be effective. There is an abundance of evidence in this context, especially for MPH and ATX. In contrast to many other drugs used by relatively large proportions of children, drugs for treating ADHD are licensed and on-label for children. Although ADHD medication is being increasingly used for adolescents and adults, not much is published on specific efficacy and safety issues in these age categories. In general, we may conclude that though stimulant use has increased over the years, there is a lack of studies on long-term effects of ADHD drugs in all ages. Since ATX is new and has been used on a relatively small scale, not much is known yet about its adverse events. This may at times bias the ATX – MPH choice discussion in favor of the first. There are few studies that provide a head on comparison between various drugs used in ADHD. Multiple studies with small and large number of subjects using different scales and methods, along with varying durations, make meta-analyses in ADHD an onerous task. Although MPH has been used for decades, physicians also need to be aware that rare and possibly severe adverse events might come up. Also, the increased longevity of ADHD medication use may give rise to new concerns, which stresses the importance of monitoring people who use this medication for such a long period.

Take home message

1. There have been recent advances in the pharmacotherapy of ADHD with studies showing that MPH, MAS and ATX are useful in children with ADHD.

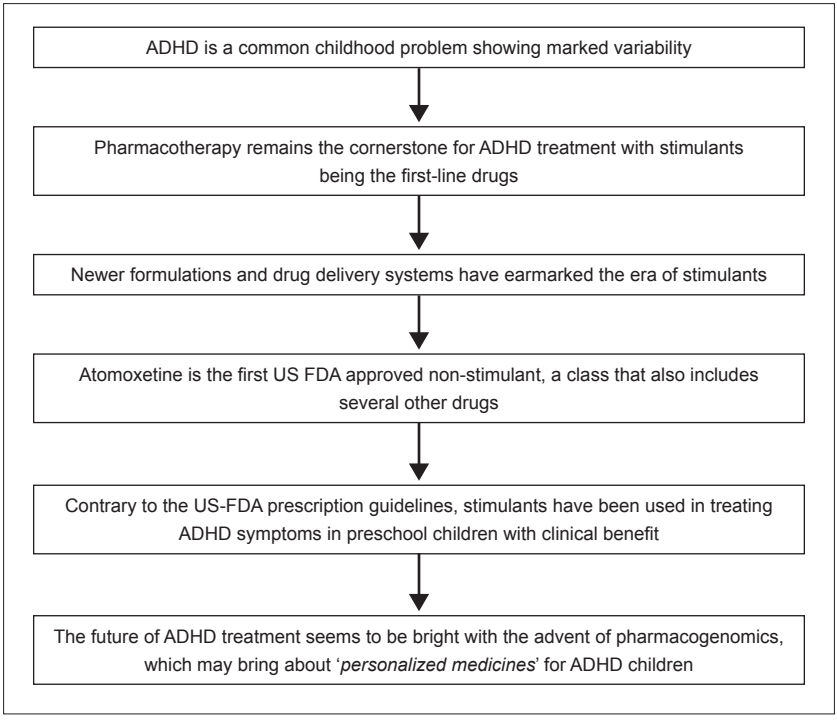

Figure 1: Flowchart of paper

2. Stringent monitoring of treatment emerging side effects with these drugs is essential when a patient is taking them for a long time.
3. There are various novel drug delivery methods available for MPH that allows optimal dosage and once a day dosing.
4. Various anecdotal case reports, case series and small trials have shown the usefulness of medications like Bupropion, Reboxetine, Clonidine and Selegiline in ADHD. These agents may be used in non-responders to MPH or ATX.
5. Compared to the earlier contrary belief, it is noted from certain studies that ADHD treatment may need initiation right in the preschool years between ages 3 to 6.
6. In the near future, Pharmacogenomics, though at an investigational stage, holds promise to individualise and personalise ADHD treatment based on patient genotype.

Conflict of interest

None declared.

Declaration

This is our original unpublished work, not submitted for publication elsewhere.

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Questions that this Paper Raises

1. Are we fully equipped with current pharmacotherapy for a complete management of ADHD?

2. What do we expect from newer drugs for ADHD – ease of dosage and better drug delivery systems, or newer mechanisms of action?

3. Is it wise to keep trying off label drugs in ADHD when US FDA approved medications fail?

4. Should ADHD be treated with medication in preschool children?

5. What is future of the treatment of ADHD with the advent of pharmacogenomics?

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