



## The Pharmacotherapeutics of Methylphenidate and Atomoxetine for the Treatment of Childhood and Adolescent Attention Deficit-Hyperactivity Disorder

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### Abstract

The most common class of drugs used to treat Attention Deficit-Hyperactivity Disorder (ADHD) are the central nervous stimulants. These drugs stimulate specific areas of the central nervous system and aim to reverse the symptoms of ADHD. Medication for ADHD can be divided into stimulants such as methylphenidate, dexamphetamine, and lisdex amphetaminedimesylate, and non-stimulants such as atomoxetine. This review evaluates and critically discusses the pharmacotherapeutics of and neuronal systems involved in two drugs - methylphenidate and atomoxetine - prescribed for the treatment of ADHD in a paediatric behaviour clinic where children are assessed and treated for ADHD and co-morbid conditions. The presentation and prevalence of ADHD in children is also discussed.

### Keywords

Methylphenidate, Atomoxetine, Pharmacotherapeutics, ADHD

### List of Abbreviations

ADHD: Attention Deficit-Hyperactivity Disorder; BNF: British National Formulary; BNFC: British National Formulary for Children; DSM: Diagnostic Statistical Manual; GABA: Gamma-Amino Butyric Acid; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography

### Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is the most commonly diagnosed neuro behavioural disorder of childhood, affecting 5% of children worldwide [1]. ADHD is characterised by levels of impulsiveness, motor activity, distractibility, restlessness and inattention that are inconsistent with the child's developmental level. Three subtypes have been recognised: inattentive, hyperactive/impulsive and combined (inattentive/hyperactive/impulsive) [2]. While ADHD is widely recognised as a disorder of childhood in twenty to thirty percent of cases it persists into adulthood and maybe accompanied by comorbid problems such as substance misuse and anxiety [3]. ADHD often occurs alongside significant psychiatric conditions which include depression and anxiety. Learning difficulties, oppositional defiance and conduct

disorders frequently co-exist with ADHD [4]. As many as one third of those diagnosed with autism display symptoms characteristic of ADHD. The two syndromes share many features, the most prevalent being attention deficit problems, impulsivity and hyperactivity. Individuals diagnosed with autism, tend to display social and

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communication difficulties and stereotyped or repetitive behaviours [5]. ADHD persists beyond childhood and into adulthood in about 40-65% of cases, affecting 4% of the adult population [6]. In adults ADHD is linked to a 25-fold increase in risk for institutionalization for delinquency, 10-fold increase of anti-social personality disorder, a 9-fold increased risk for imprisonment, and up to a 5-fold increase for drug abuse [7].

The Diagnostic Statistical Manual (DSM), published by The American Psychiatric Association sets out criteria for the classification of mental disorders. The most recent edition (DSM-5) has changed how ADHD is diagnosed and there is now a shift in the way ADHD is classified. It will no longer be grouped with conduct disorder and oppositional disorder, but recognised as a neurodevelopmental disorder. Emotional outbursts which previously came under the symptoms of ADHD now come under bipolar disorder [8]. There is no single, simple or definite test for ADHD. For a diagnosis to be made, a specialist assessment by a paediatrician or psychiatrist is required. The diagnosis is made by recognising patterns of behaviour, observations of the child ideally at home and in school. Some children may require specialised tests by a clinical or educational psychologist and occasionally a computerised test may be carried out to aid diagnosis. Given the prevalence of ADHD, and the societal and personal impact of the condition from childhood to adulthood, effective treatment is crucial. The majority of children who receive specialist treatment tailored to their needs may benefit considerably.

## Review

### Pathobiology of ADHD

From the 1980s ADHD was thought to be due to small deficits in the frontal and basal ganglia regions of the brain [9]. This hypothesis was posed as a result of the effectiveness of psycho-stimulants, such as methylphenidate which had been shown to affect levels of frontal and striatal dopamine in animals. The theory was reinforced by the fact that frontal and striatal animal and human lesions cause ADHD-like symptoms. A greater understanding of ADHD, and the parts of the brain affected by it, has been made possible by modern neuroimaging techniques such as Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI). These studies not only showed earlier theories to be correct but also showed ADHD to be more than a problem of frontal and striatal deficits [10]. Neuroimaging studies have consistently demonstrated that relative to "normal" brains, children and adults with ADHD have abnormalities in several late developing fronto-striatal, temporo-parietal and fronto-cerebellar neural networks known to mediate the self-monitoring, attention, inhibitory and

timing functions that are compromised in ADHD. Abnormal brain structure has been observed in children and adults with ADHD - in total cerebral volumes, several frontal brain regions, in the basal ganglia, the splenium of the corpus callosum and the cerebellum [10,11]. Age was also associated with structural deficits, that is, the volume of basal ganglia in older patients was found to be within normal limits. This suggests that children may grow out of their striatal brain deficits. However in other brain regions, such as the frontal and temporo-parietal areas, adults with ADHD have been shown to suffer brain impairment similar to that of children with ADHD, suggesting that brain deficits in these regions persist into adulthood [12]. Longitudinal imaging studies discovered that compared with non-ADHD peers, the structural abnormalities observed in children with ADHD may be due to a delay in maturation [13]. This research confirms a long-held theory that ADHD results from a delay in brain maturation. Neuro-imaging has shown that ADHD patients not only display under-activation in the dorso-lateral and inferior frontal cortex and the basal ganglia, but also in other areas of the brain that are important in the regulation of inhibition, attention, motivation and affect [10,11].

Further studies have indicated that not only are isolated areas of the brain affected in ADHD but communication between the different regions is also affected. Structural connectivity studies of ADHD patients have shown deficits in late developing white matter tracts connecting the front-striatal, fronto-parietal, fronto-cerebellar and parieto-occipital regions [14]. Recent analyses that investigated the extent to which brain regions work together have indicated that brain circuits are less interconnected in ADHD, both during rest and when performing cognitive tasks [14].

Nerve cells conduct electrical signals throughout the body and have particular intercellular connections with other cells and tissues [15]. Nerve cells comprise dendrites whose function it is to receive information from other cells and pass the information to the cell body [16]. In the autonomic nervous system communication between nerve cells involves the connection of two neurons in tandem. As an action potential travels along the first nerve it encounters a structure at the end called a synapse. The synapse is essentially a space called the synaptic cleft, which must be bridged for the impulse to reach the next nerve. The nerve carrying the original impulse is called the pre-synaptic neuron while the nerve receiving the impulse on the other side of the synaptic cleft is called the post-synaptic neuron. Chemicals known as neurotransmitters are released into the synaptic cleft when an impulse reaches the end of the pre-synaptic neuron which causes the impulse to be generated [17]. The role

of the neurotransmitter substance is to transfer signals between the neurons across the synaptic cleft [18]. The main neurotransmitters in the brain are dopamine, norepinephrine, 5-hydroxytryptamine (serotonin), Glutamate,  $\gamma$ -Amino Butyric Acid (GABA) and acetylcholine. It is now believed that more than one neurotransmitter is released during this process and that there are two types of neurotransmitter: inhibitory and excitatory [18]. As the name suggests excitatory neurotransmitters stimulate brain activity whereas inhibitory neurotransmitters exert a calming effect on the brain. When excitatory neurotransmitters are overactive, inhibitory neurotransmitters are reduced. Having travelled across the synaptic cleft the neurotransmitters bind to receptor sites (similar to a key in a lock) and various physiological responses are initiated [15]. Studies using PET have shown that ADHD patients have deficits in underlying neurotransmitter systems, most importantly the dopamine system [19].

Genetic studies have highlighted consistency in showing certain genes influencing susceptibility to ADHD. Much of the data focuses on the dopamine D4 receptor gene which encodes a protein receptor that mediates the postsynaptic action of dopamine [20]. Dysfunction of catecholamine, and particularly dopamine neuronal systems, has been postulated to be involved in ADHD [21]. Dopamine has an important role in attentional, psychomotor, reinforcing and rewarding behaviours that are lacking in ADHD. Methylphenidate and amphetamine have been extensively used to treat ADHD to block dopamine and norepinephrine transporters thereby enhancing catecholamine neurotransmission [22].

## Methylphenidate

Stimulant medication, in the form of the piperidine derivative methylphenidate, accounts for the majority of the prescribed medication for ADHD [23,24]. Methylphenidate's mode of action in ADHD is not fully understood however it is believed that methylphenidate activates the cortex and brain stem arousal system. The mode of action is to increase the quantity of norepinephrine and dopamine at the synaptic cleft. Studies have shown that methylphenidate blocks the reuptake of dopamine and norepinephrine into the presynaptic neuron resulting in prolonged effects at the dopamine receptor [25].

In 2001 Jensen and colleagues published the results of one of the largest and longest multimodal treatment studies in ADHD. The study examined the efficacy of stimulant medication alone or in combination with behavioural therapy and involved 579 children over a 14 month period. The dosing titration method and patient response to methylphenidate using the patient data was evaluated. The efficacy rate was found to be 77% with an

the optimal dosage range of 10-50 milligrams per day [26].

Stimulants are administered orally, absorbed rapidly and completely from the gastrointestinal tract, and then cross the blood brain barrier into the central nervous system. Maximal clinical effect of stimulants is achieved approximately two hours post administration [27]. Absorption parallels with the acute release of neurotransmitter at the synaptic clefts [28]. Methylphenidate is extensively metabolised by de-esterification to alpha-phenyl-piperidine acetic acid which has no pharmacological activity [29]. Initially, timing the administration of stimulant medication was reported as being one of the most challenging aspects of managing children with ADHD. Methylphenidate acts rapidly but is of short duration requiring administration 2-3 times daily to maintain adequate serum concentrations to permit school and homework to be completed. The effect should be allowed to diminish in time for a normal sleep pattern. There was concern and reluctance on the part of schools about administering medication throughout the school day which led to the development of the first extended release wax-matrix products in the mid-1980s. These drugs are effective for 6-8 hours which should cover the school day, however some children may require an additional dose at midday to provide adequate coverage in the late afternoon and early evening. The first of these modified release drugs to be developed was Concerta XL<sup>®</sup> (modified release methylphenidate hydrochloride). The BNF states that prescribers should specify the brand to be prescribed since different versions of modified-release preparations may not have the same clinical effect [30] therefore in this paper discussion of modified release methylphenidate hydrochloride refers only to Concerta XL<sup>®</sup>.

Concerta XL<sup>®</sup> is an extended-release tablet which uses osmotic pressure to distribute methylphenidate at a controlled rate [31]. The tablet contains an osmotically active tri-layer core surrounded by a semi-permeable membrane with an outer drug overcoat. The outer drug coat dissolves once it is in the relatively water-rich environment of the gastrointestinal tract. This process happens within the first hour post-administration and provides an immediate effect.

Fluid then moves into the osmotic core which causes a polymer to expand and push the drug through a hole drilled into the drug layer of the tablet. The membrane is responsible for controlling the rate of water penetration and subsequent drug delivery in due course. It is designed so that 22% is released immediately and 78% is released over time [28]. Concerta XL<sup>®</sup> is taken once daily and provides effective serum methylphenidate con-

centrations over a 10-12 hour period, equivalent to immediate release methylphenidate given three times daily [32]. As it is designed to release the drug at a controlled rate, the tablet must pass through the gastro-intestinal tract unchanged therefore patients must be able to swallow the tablet whole (membrane intact) with liquid; for this reason it may not be appropriate to prescribe for use in dysphagia or if gastro-intestinal lumen restricted [30]. The half-life of methylphenidate in adults following administration of Concerta XL<sup>®</sup> is approximately 3.5 hours. According to Hill and Adrian [33], Concerta XL<sup>®</sup> is metabolised in the tissues to ritalinic acid and then eliminated from the body by urinary excretion with the drug is almost completely eliminated from the body within 24 hours. When commencing Concerta XL<sup>®</sup>, careful titration of the dose is necessary so patients should be commenced on the lowest dose possible. An evaluation of the patient's cardiovascular status, including blood pressure and heart rate, should be made and used as a baseline in addition to a comprehensive medical history.

### Atomoxetine

Atomoxetine was the first non-stimulant drug approved for the treatment of ADHD. Atomoxetine is one of a number of drugs identified as a specific blocker of the presynaptic transporter. It is classified as a selective norepinephrine (noradrenaline) reuptake inhibitor, as it inhibits the reuptake of presynaptic norepinephrine by capturing norepinephrine present in the synaptic cleft and transporting the norepinephrine back into the presynaptic nerve terminal. It has been shown to increase the release of norepinephrine and dopamine 3-fold in the prefrontal cortex without changing dopamine amounts in other parts of the brain unlike stimulants [34]. Atomoxetine is approved for use in children, adolescents and adults although its efficacy has not been studied in children under 6 years. The recommended doses range as follows: children aged 6-17 years (weighing up to 70 kg) 500 micrograms/kg daily for first 7 days with dose increased according to response, maintenance dose 1.2 mg/kg daily; children aged 6-17 years (weighing 70 kg and over) 40 mg daily for first 7 days with dose increased according to response, maintenance dose 80 mg daily; adult (weighing up to 70 kg) 500 micrograms/kg daily for first 7 days with dose increased according to response, maintenance dose 1.2 mg/kg daily; adult (weighing 70 kg and over) 40 mg daily for first 7 days with dose increased according to response, maintenance dose 80-100 mg daily; for all patients, the total daily maintenance dose may be given either as a single dose in the morning or two divided doses with the last dose no later than early evening [30]. It has an advantage over stimulant treatments for ADHD as it is less likely to be abused. It is not scheduled as a controlled substance like methylphenidate and has

been proven in clinical trials to offer 24 hour coverage of symptoms associated with ADHD in adults and children. The most common side effects are gastrointestinal including nausea, vomiting, decreased appetite, weight loss, tiredness and fatigue [35]. Fortunately these symptoms are transient and treatment with atomoxetine is favourable to compared stimulants because of its relatively long duration of action with less exacerbation of tics in patients prone to developing this associated side effect [23]. Atomoxetine improves patient motivation, energy levels and self-perception; it also has a positive effect on social functioning, mood and attention [36].

Atomoxetine is administered orally and is rapidly and almost completely absorbed from the gastrointestinal tract. Absorption is minimally affected by food. At therapeutic concentrations 98% of atomoxetine in plasma is bound to protein, primarily albumin [38]. Cytochrome P450 (CYP450) enzymes are essential for the metabolism of many medications. Although there are in excess of 50 enzymes in the P450 class, 6 enzymes are responsible for metabolising 90% of drugs. The two most important enzymes are CYP3A4 and CYP2D6. Atomoxetine is metabolised mostly in the liver by the cytochrome enzymes, primarily the CYP2D6 pathway to 4-hydroxyatomoxetine [39]. Greater than 80% of the dose of atomoxetine is excreted in the urine as 4-hydroxyatomoxetine-O-glucuronide while approximately 13-22% is excreted in the faeces [39]. Atomoxetine can take 6-8 weeks to exert its pharmacological effects. Full benefits may not be observed for 6 weeks and in some cases 10-12 weeks. Some children, however, respond quickly and may be sensitive to the medication with side effects such as abdominal complaints occurring in approximately 20% of children; liver complications have been reported but are extremely rare [40].

### Conclusion

The pharmaceutical industry has invested in research and development for new preparations of stimulant medications for the treatment of ADHD. Treatment of ADHD has been vastly transformed by the development of longer acting stimulant formulations which have significantly improved the management of adults, adolescents and children with ADHD. The development of longer acting stimulants has removed the burden of administrations of medication and hence improved the treatment of ADHD symptoms during school hours which previously had sometimes posed challenging. The new generation of stimulant and non-stimulant medications allows patients to take control of their symptoms. Many patients may tailor medication to suit their needs, for example students can increase medication if they require more concentration at certain times of the day when studying for exams. Children exhibiting mild to

moderate symptoms, which may only cause difficulties in school, benefit from stimulant formulations with 6-8 hours duration of action. For children with more severe or prolonged ADHD symptoms, use of a longer acting preparation may be necessary. Atomoxetine may be a good alternative for patients who are unable to tolerate stimulant medication because of side effects such as tics or anxiety. Atomoxetine is indicated for the long-term treatment of ADHD in children, adolescents and adults and has been proved effective for controlling symptoms that last throughout the day and into the evening with a decreased risk of user rebound. An added benefit of atomoxetine is its non-controlled status, which makes it easier for patients requiring more than one month supply and making it less likely to be abused. The pharmaceutical properties of medication for ADHD highlight the specialist knowledge required to make prescribing decisions and also the need to make careful health assessments and monitor health while the patient remains on medication.

## Competing Interests

The authors declare no competing interests.

## Authors' Contributions

All authors have been involved in drafting the manuscript and/or revising it critically for important intellectual content and have given final approval of the version to be published.

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