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ADHD & Pharmacotherapy: Past, Present and Future:

A Review of the Changing Landscape of Drug Therapy for Attention Deficit Hyperactivity Disorder

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Abstract

Attention deficit hyperactivity disorder (ADHD) is the most common neurobiological disorder in children, with a prevalence of ~6–7%^{1,2} that has remained stable for decades². The social and economic burden associated with patients³, families, and broader systems (healthcare/educational) is substantial, with the annual economic impact of ADHD exceed \$30 billion in the US alone⁴. Efficacy of pharmacotherapy in treating ADHD symptoms has generally been considerable with at least ¾ of individuals benefitting from pharmacotherapy, typically in the form of stimulants⁵. In this review, we begin by briefly reviewing the history of pharmacotherapy in relation to ADHD, before focusing (primarily) on the state-of-the-field on themes such as biophysiology, pharmacokinetics, and pharmacogenomics. We conclude with a summary of emerging clinical and research studies, particularly the potential role for precision therapy in matching ADHD patients and drug types.

Keywords

ADHD; pharmacotherapy; pharmacology; drug; medication; adverse events

PAST

The most common and effective medications are methylphenidates and amphetamines. Atomoxetine and the α -adrenergic agonists are also widely-used, while tricyclics such as modafinil and Wellbutrin are less common and typically less effective⁶.

First synthesized in 1887, amphetamine (alpha-methylphenethylamine) was not studied clinically until 1927, initially as an artificial replacement for epinephrine⁷. For several years,

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it was developed primarily as a bronchodilator, though recognition of stimulant properties subsequently led to a broadening of clinical scope across several dozen conditions⁷. In 1937, the effects of Benzedrine sulfate treatment were first documented in 30 children (21 boys, 9 girls; 5–14 years old) with a range of behavior disorders. The amphetamine was administered as a treatment for headache, but consequent behavioral changes were marked, including a “drive” to accomplish as much as possible and improvement from a social viewpoint⁸. A larger follow-up study (n=100) in 1941⁹ was less sweeping in its conclusions, but nevertheless documented “subdued” social impairment in 54% of the children studied¹⁰. By this point, amphetamines had been proposed as a treatment for a range of conditions, including schizophrenia, addiction, cerebral palsy, low blood pressure, and seasickness⁷, with less focus on ADHD¹⁰.

It was not until the 1950s that research in stimulant drugs became truly relevant to ADHD (or precursors such as hyperkinetic disease, hyperkinetic impulse disorder, and minimal brain damage¹¹). By then, the amphetamine derivative, methylphenidate, had been synthesized (1944)^{6,12}, and subsequently marketed as ‘Ritalin’^{11,13}. These developments coincided with the waning influence of psychoanalysis, and the belief that behavioral disorders had little or no biological basis¹¹. In 1957, an important study addressing *Hyperkinetic impulse disorder in children’s behavior problems*, defined hyperactivity as a potentially biological phenomenon, as well as delineating a role for stimulant drugs in its treatment. A surge of studies followed cataloguing the treatment of hyperactive children with stimulant medication, which was maintained as a therapy for the newly-defined Hyperkinetic Reaction of Childhood (DSM-II, 1968¹⁴) and Attention Deficit Disorder (DSM III, 1980¹⁵). Currently, stimulant medication is the most common treatment for ADHD, where a diverse catalogue of delivery mechanisms has facilitated development of longer-acting compound preparations. Alternative drug treatments include norepinephrine reuptake inhibitor and α -adrenergic agonists.

PRESENT

While the literature is consistent in confirming the effectiveness of pharmacotherapy in treating ADHD, it is notable that mechanisms of action (MOAs) are generally poorly understood and underdeveloped. Numerous studies have reported differential effects for ADHD medications in terms of associated neurobiology and relevant neurotransmitter systems. Stimulants in particular have reportedly affect a plethora of brain regions¹⁶, neurotransmitters¹⁷, and gene regulators^{18,19}. Atomoxetine and the α -agonists have more targeted effects and this may be reflected in the lower response rates. Table 1, adapted from Elia *et al.* (2014)⁶, summarizes approved medications worldwide including methylphenidate, amphetamines, α -adrenergic agonists, and a selective norepinephrine reuptake inhibitor. The most effective pharmacotherapies remain methylphenidate and amphetamine compounds.

Effectiveness and Effect Size

Relative to other psychiatric diseases, ADHD is often considered a poster-child in terms of the effectiveness of drug treatments. Indeed, a large-scale meta-analysis by Leucht *et al.* (2012) that included 16 drugs in 8 psychiatric disorders, showed that methylphenidate and

amphetamine are among the most effective psychotropics, with only lithium (major depressive disorder, maintenance therapy) showing comparable results. The same study reported a less robust effect size for atomoxetine/ADHD. In total, between 75% and 90% of patients have been reported to respond to some form of pharmacotherapy, although many patients do not necessarily respond to the first drug regimen. Methylphenidate and amphetamines are most widely-prescribed for ADHD, and clinical trials have repeatedly demonstrated their efficacy across short- and long-acting preparations, and across ages ranging from preschool to adulthood^{20–24}.

Table 2 (Elia *et al.*, 2014)⁶ summarizes the effect size of relevant ADHD treatments. In addition to stimulants, atomoxetine and α -adrenergic agonists are also effective in managing ADHD symptoms, though, as outlined, relevant effect sizes are comparably smaller to those of stimulants. A caveat being that often patients prescribed atomoxetine/ α -adrenergic agonists may already have failed to respond to stimulants, so it may not be a strictly representative cohort.

Beyond ADHD core symptoms, pharmacotherapy has been associated with improved quality of life²⁵, decreased risk of developing depression^{26,27} and anxiety/disruptive disorders over a 10 year period²⁷, paralleled by improved grade retention²⁷. A 2012 study of 25,656 ADHD patients from the Swedish national register compared criminal convictions across a three-year period and found a significant decrease in the rate of criminality while patients were ADHD medication versus the same patients unmedicated²⁸.

Neurobiological Correlates

The mechanisms by which those medications listed in Table 1 impact upon ADHD symptoms are poorly understood. Several studies report a role for methylphenidate in inhibiting dopamine transporters in the cortex and striatum^{29,30}. The same drug may also inhibit the norepinephrine transporter in the cortex³⁰. The MOA may relate to amphetamine stimulating leakage of dopamine and norepinephrine into the synaptic cleft. In turn, this may inhibit their degradation and inactivate the storage protein pump. Ultimately, this would increase the extracellular availability of both neurotransmitters and also extracellular serotonin³¹.

Stimulants—Improvements in attention associated with taking methylphenidate are correlated with increased dopamine levels in the ventral striatum, prefrontal cortex (PFC), and temporal cortex³². Methylphenidate administration has also been associated with normalizing underactive frontocingulate networks³³ and striatal areas³⁴ and increased frontoparietal connectivity for working memory³⁵. Other neurobiological changes observed in relation to methylphenidate administration include enhanced error-detection associated with the dorsal anterior cingulate cortex and inferior parietal lobe³⁶, and optimized speed-of-reaction related to (pre-) motor cortex³⁷. A number of other gross neurobiological effects have been associated with taking methylphenidate, including increased activation in the caudate, cerebellum, midbrain, substantia nigra, thalamus³⁸, and many others. Wong *et al.* (2012)³⁵ report increased functional connectivity in the anterior cingulate, ventrolateral PFC, and precuneus, which is also associated with working memory.

Atomoxetine increases the availability of norepinephrine (noradrenaline) and dopamine in the PFC³⁹, selectively inhibiting relevant transporters presynaptically. It also an NMDA receptor antagonist, thereby altering glutamatergic transmission⁴⁰. Unlike stimulants, atomoxetine is not strongly associated with striatal effects, and is less likely to be abused (full effect also takes 4–6 weeks). Neurobiological correlates of atomoxetine administration include increased regional cerebral blood flow in the cerebellar cortex, and decrease blood flow to the midbrain, substantia nigra and thalamus³⁸. Enhanced inhibitory control following atomoxetine has also been associated with increased activation of the right inferior frontal gyrus⁴¹.

α -Adrenergic Agonists—Guanfacine inhibits cyclic AMP, closing hyperpolarization-activated (HCN) cyclic nucleotide-gated channels and increasing functional connectivity in the PFC. By blocking/knocking-down HCN1 channels in the PFC therefore, guanfacine can improve working memory⁴². Guanfacine has been shown to increase activation in the dorsolateral PFC. It is noteworthy that glutamatergic synapses have heteroreceptors that are inhibitory α 2A-adrenoceptors⁴³, and it is possible (though admittedly speculative) that clonidine and guanfacine are effective by reducing presynaptic glutamate release in the PFC. This hypothesis is supported by a recent study by Miller *et al.* (2014)⁴⁴, which showed abnormal glutamate signaling in the signaling in PFC and striatum of the spontaneously hypertensive rat model of ADHD. The potential role for glutamatergic medication in treating ADHD is discussed further below.

Safety

As illustrated in Table 3, ADHD medications have been associated with a range of common and rare adverse effects⁴⁵, that correlate with age/developmental-stage²¹. While many adverse events are often transient and dose-dependent⁴⁶, effects such as appetite loss may persist for years⁴⁷. Adverse events may also be genotype-specific, with, for example, *CYP2D6* poor metabolizers at greater risk with atomoxetine⁴⁸.

As outlined, cardiovascular effects are among the most serious adverse events. Sudden death, reported in four children taking clonidine, are particularly concerning, but investigations into these deaths attribute likely cause to pre-existing cardiac conditions and concomitant drug treatment⁶. Bradycardia, however, has been consistently reported with clonidine – in up to 17.5% of patients on mono- or combined-therapy with stimulants, *vs.* 3.4% in non-users⁴⁹. The same study also found drowsiness to be a widespread effect of clonidine use, but this may resolve in <2 months. A 2012 study of antipsychotics by Winterstein *et al.* (2012)⁵⁰ documented 1,219,847 children and 95 events (66 excluding ventricular arrhythmia), and reported an adjusted odds ratio of 0.62 for stimulant *vs.* non-stimulant use. This corresponds to corresponding an adjusted incidence rate of 2.2 *vs.* 3.5 per 100 000 patient years for stimulant use *vs.* non-use, and is essentially negligible.

With atomoxetine, liver toxicity is rare but not trivial. Bangs *et al.* (2008)⁵¹ studied 7,961 children and adult patients taking atomoxetine during clinical trials, and reported 41 patients with documented hepatobiliary events, but none of which progressed to liver failure. The same study identified 351 spontaneous adverse hepatic events, of which three suggested

atomoxetine as a probable cause (of the remainder, 69 were categorized as unrelated to atomoxetine, 133 as confounding factors, 146 too little information). One of these three had a positive re-challenge. Additionally, Lim *et al.* (2006)⁵² presented cases studies of two children with acute hepatitis following atomoxetine. In one, no competing diagnosis was found, and liver injury resolved by discontinuing atomoxetine. In the second, evaluation suggested type 1 autoimmune hepatitis, which also ameliorated with discontinuation and concomitant immunosuppressive therapy.

Self-injury/ideation is another adverse event on the more serious spectrum. Such ideation has been reported in ~1.5% of patients prescribed atomoxetine or stimulants, and monitoring for such effects is warranted. Additional limitations include generally short-half lives that diminish behavioral efficacy to several hours/day for the stimulants and drug interactions *via* P450-2D6 for atomoxetine.

6. Pharmacogenomics (PGx)

Several reviews have cataloged the role of genetic variants in mediating responses to ADHD medication, indicating mixed and inconclusive results^{53,54}, and suggesting that, similar to the disease itself, drug response is a highly complex trait.

Indeed, methylphenidate has been reported (in rats) to upregulate expression of >700 genes in the striatum involved in neural/synaptic plasticity including neurotransmitter receptors, proteins responsible for transport and anchoring, and many others⁵⁵. Thus, a reason why stimulants show efficacy in most individuals may be due to the fact that they affect expression in numerous genes throughout the brain, thus impacting on potentially numerous variants. For similar reasons, response rates may be lower for the more selective medications such as atomoxetine and α -adrenergic agonists, potentially with fewer variants involved.

The majority of PGx-based studies have focused on existing ADHD medications, primarily methylphenidate, with the goal of identifying specific biomarkers of drug response, which are reviewed briefly here (see also Bruxel *et al.*, 2014⁵⁶). One exception to this approach is a study from our group, which has used results from genomics analyses to identify novel drug targets for a genome-stratified ADHD sub-cohort.

Dopaminergic system—Interactions between *DAT1* genotypes and methylphenidate response are among the most-widely studied in terms of ADHD and PGx. The dopamine active transporter (DAT) protein encoded by *DAT1* is widely expressed in the dopaminergic system, particularly in projections to the nucleus accumbens and striatum⁵⁷. Several variable number tandem repeats (VNTRs) have been identified for *DAT1*, with the 9-repeat and 10-repeat alleles. Froehlich *et al.* (2011)⁵⁸ reported that 10R carriers vs. non-carriers are poorer responders to methylphenidate, with an effect size of 0.59–0.64 (though $n=89$). Pasini *et al.* (2013)⁵⁹ compared responses of 108 drug-naïve patients to methylphenidate treatment across a 24-week period. The sample was stratified into 9R/9R, 9R/10R, and 10R/10R sub-cohorts, with various outcomes (response inhibition, working memory, planning) assessed longitudinally. Patients with the 10R genotype had consistently improved response inhibition, which was not seen after therapy was discontinued. Improvement in planning and working memory were also noted and maintained, but it is again difficult to draw firm

conclusions given the sample size. This would seem substantiated by a meta-analysis by Kambeitz et al., 2014 (n=1572)⁶⁰, which found no evidence of a genotype-specific response to methylphenidate treatment ($P>0.5$). Similarly, VNTRs in the dopamine receptor D4 (DRD4) have been studied, again with no strong evidence of a genotype-specific response to methylphenidate⁵⁶.

Other systems—ADHD PGx interactions have also been studied in relation to the norepinephrine transporter gene (*NET1*), though again results are inconclusive. Kim et al. (2010)⁶¹ compared methylphenidate response between A-3081T (rs28386840) and G1287A (rs5569) genotypes in 112 Korean children, where Clinical Global Impression-Improvement scores were higher in the former (61.4%) compared to the latter (37.9%), though again the study is underpowered and was not replicated by a subsequent study⁶². Several other studies of *NET1* effects in different Asian populations have also been reported and are similarly inconclusive.

A large range of other proposed ADHD-PGx candidate genes include *ADRA2A*, *COMT*, *TPH2*, *DBH*, *5-HTT*, *BDNF*, *SNAP25*, and *LPHN3* (review at Bruxel et al., 2014⁵⁶), but as yet none constitute a stand-out model for targeted/precision intervention. Below, we discuss a different approach to the PGx model, in which genomics results can be used to guide development of novel therapeutics (as opposed to stratify response to existing medications).

FUTURE

A recent study sequenced 202 genes (including dopaminergic, adrenergic, glutamatergic, histaminergic and cholinergic receptor genes—considered potential drug targets) in approximately 14,000 individuals (not ADHD), and discovered that 95% of genetic variants were not common but rare (occurring in less than 0.5% of the population) with 74% found in only one or two individuals⁶³. This further suggests that—not only for ADHD but for other disorders as well—pharmacotherapeutic targets of the future are likely to focus on rarer genetic variants.

To this end, a large-scale, genome-wide study from our group compared copy number variations (CNVs) in ADHD cases (3,500) vs. controls (~13,000) revealed that rare, recurring CNVs impacting specific GRM genes (i.e. *GRM1*, *GRM5*, *GRM7*, and *GRM8*) encoding for metabotropic glutamate receptors (mGluRs) were found in ADHD patients at significantly higher frequencies compared to healthy controls⁶⁴. The large effect sizes (with odds-ratios of >15) suggest that these mutations likely are highly penetrant for their effects on ADHD. Single cases with *GRM2* and *GRM6* deletions were also observed that were not found in controls.

When genes in the signaling pathway of GRM genes (i.e. a GRM/mGluR-network) were assessed, significant enrichment of CNVs was found to reside within this network in ADHD cases compared to controls. Our group recently identified 228 genes within the GRM gene networks based on the merged human interactome provided by the Cytoscape Software¹⁸. A network analysis of the mGluR pathway found that in the EA population of approximately 1,000 cases and 4,000 controls, genes involved with GRM signaling or their interactions are

significantly enriched for CNVs in cases ($P = 4.38 \times 10^{-10}$), collectively impacting ~12% of the ADHD cases, corrected for control occurrence (Figure 1B). These data suggest that GRMs may serve as critical hubs that coordinate highly-connected modules of interacting genes, many of which harbor CNVs and are enriched for synaptic and neuronal biological functions. Thus, we have identified several rare recurrent CNVs that are overrepresented in multiple independent ADHD cohorts that impact genes involved in glutamatergic neurotransmission, which is essential for the developing brain and normal brain function. These results suggest that variations involving mGluR gene networks of the brain contribute to the genetic susceptibility of ADHD. Further, disrupted mGluR signaling/activity in ADHD in a sub-cohorts can be identified based on genetic profiling of their genes within this GRM-network and selectively drug-targeted.

Discovering efficacious novel therapeutics for neuropsychiatric disorders has proven to be difficult in part because of a lack of clear understanding of their molecular etiologies⁶⁵. Our group's research in ADHD is focused on characterizing genetic variants that disrupt a specific pathway (the glutamatergic pathway) involving neurotransmission in the brain. We have identified a small molecule compound, NFC-1, which previously underwent extensive clinical testing⁶⁶ and was shown to have stimulatory activity towards mGluR pathways^{67–69}, producing notable psychoactive effects in animal models^{70,71}. The drug was originally developed in the late 1980s for treating dementia-related cognitive impairment, but was eventually abandoned during Phase III trials in dementia. The drug was shown to be safe and well-tolerated. Studies in primates and rodents also demonstrated no signs of addiction or dependency to the drug⁷². Ultimately, we aim to reposition NFC-1 for use as a targeted therapy for ADHD in patients who are “biomarker positive” for the mGluR/GRM gene network (i.e., any mutation, CNV or SNV that is significantly enriched (>2 fold) in ADHD patients in comparison with controls. An Investigational New Drug (IND) application was recently approved by the FDA on and the first 30 patient trial in mGluR biomarker positive patients began in January 2015 and completed recruitment in April, 2015 (www.ClinicalTrial.gov).

Clinical Trial in mGluR biomarker positive patients with ADHD

Through a comprehensive survey of published studies and public databases, we identified drug candidates that act on the mGluR pathway and could potentially rescue the underlying neurogenetic defects in patients with the ADHD. As discussed, our network analysis directly implicates the known action of NFC-1 as a potential pharmacological agent that may be efficacious in patients with ADHD due to highly penetrant genetic defects in the mGluR pathway. NFC-1 is not currently approved for any indication; however it is known to exhibit nootropic effects and have cognition-enhancing properties. Its safety profile has been well established, having undergone Phase I, II and III clinical trials for other indications. NFC-1 is a member of the piracetam-like drug family, and the published literature on the piracetam-like drug confirms that these compounds in clinical use are well-tolerated, generally safe and effective for their respective indications^{73–75}. Moreover, this class of compounds has also been used in studies involving children^{75,76}.

NFC-1, which exhibits stimulatory activity for all three groups of mGluRs, has been shown to improve cognitive functions in animal models. Thus, NFC-1 presents an important candidate to explore for use in restoring mGluR activity in those ADHD patients exhibiting rare mGluR gene network mutations. Based on NFC-1's safety/tolerability profile, it is highly unlikely that it will possess the risks and side effects associated with conventional ADHD medications. Also, a pharmacogenomics approach, where efficacy of NFC-1 is assessed in relation to the patients' genomic profile, will determine whether responders can be segregated from non-responders, which would be a significant improvement compared to current non-stimulant, targeted therapies (atomoxetine, guanfacine) for which responders cannot be prospectively identified. NFC-1 previously entered phase III clinical trial in adult dementia patients with cerebrovascular diseases but the program was suspended when the drug did not reach the defined efficacy endpoints, although safety expectations were met.

Pharmacokinetics in elderly *versus* young adults

Pharmacokinetic studies of NFC-1 in elderly and young subjects have been published⁷⁷. Fourteen healthy male volunteers (7 elderly subjects aged 68–79 years and 7 young subjects aged 20–32 years) were included in the study (Table 4). In a parallel group design, a tablet containing 100 mg NFC-1 was administered orally after breakfast. The maximum plasma concentration (C_{max}) was higher in the elderly (3.06 $\pm$ 0.69 vs. 2.13 $\pm$ 0.34 micrograms/ml, the elderly *vs.* the young, mean $\pm$ SD, p = 0.0117) and area under the plasma concentration curve (AUC) was also higher in the elderly (24.6 $\pm$ 4.4 vs. 14.4 $\pm$ 3.1 micrograms-hr/ml, p = 0.0006). A significant correlation was found between renal clearance of NFC-1 and creatinine clearance of each subject (r = 0.583, p = 0.0364). These observations indicate that the plasma concentration of NFC-1 will increase in elderly subjects mainly due to a decrement in renal clearance of the drug.

We will complete the first clinical trial in adolescents aged 12–17 years, using 4 active doses (50mg bid; 100mg bid; 200mg bid and 400mg bid) as well as placebo. The results from the study will be made available later this year. We believe this approach is indicative of a new model to ADHD precision medicine, in which genomics are used to propose novel drugs for targeted treatment.

Conclusion

It is clear that traditional drug treatments for ADHD have been largely effective, but considerable work remains to be done to elucidate methods of action. Genomics are beginning to play a larger role in such efforts, and technological advances in the past decade have accelerated identification of candidate variants associated with ADHD susceptibility. In particular, these approaches can rapidly feed-forward to translational pipelines, offering further opportunities to target treatments to genomically-characterized cohorts. One recent approach has been to target individuals with specific variants in glutamatergic pathways with a clinical trial now ongoing. Accelerating cost reductions and higher outputs of genotyping/sequencing approaches makes the identification and eventual targeting of these and potentially other transmitter systems (e.g. dopaminergic/noradrenergic) a real possibility, offering cause for optimism as we navigate the precision medicine era.

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Figure 1. GRM Receptor Gene Interaction Networks and ADHD: GRM receptor genes are shown as large diamonds, and genes within two degrees of interaction are shown as smaller circles. Shapes are colored to represent CNV enrichment: Dark red = deletions enriched in cases; Light red = deletions enriched in controls; Dark turquoise = duplications enriched in cases; Light turquoise = duplications enriched in controls; Gray = diploids devoid of CNVs. Lines: Thick blue dashed lines highlight edges connected to at least one GRM gene; Thin gray lines represent all other gene interactions. Blue shaded ellipses: Highly-connected modules enriched for significant functional annotations. From Elia *et al* (2012)⁶⁵

Table 1

Pharmacotherapy for ADHD by Medication Subtype and Geographical Location: The most effective include methylphenidate and amphetamine compounds. Adapted from Elia *et al.* 2014.

Note (dosing/discontinuation): Dosing is typically (but not universally⁷⁸) weight-based. With stimulants, optimal dosing is achieved by starting at the lowest dose and titrating based on efficacy/tolerability. The same is true for guanfacine and clonidine. With atomoxetine, weight help establish a maximum dose of 1.2–1.4 mg/kg/day.

Discontinuing stimulants and lower doses of atomoxetine does not require tapering. However, to prevent rebound and increased blood pressure, tapering is recommended for α -agonists.

Medication*	Geographical Location
1. Short-Acting Methylphenidate (MPH)	
MPH	USA, Canada, Europe, China, India, Taiwan, Australia/New Zealand, Africa
- MPH	Europe, China, India, Taiwan, Australia/New Zealand, Africa
- Ritalin® (Novartis)	USA, Canada
- Methylin® (Shinogi)	USA
- Metadate® (UCB)	USA
- Hytonin (Health Pharmaceutical Co.)	Taiwan
- Rubifen (PHARMAC)	Australia/New Zealand
Dexmethylphenidate (DexMPH)	
- Focalin XR® (Novartis)	USA
2. Longer-Acting MPH	
MPH	
- Medikinet Retard (Flynn)	Europe
- Equasym (Shire)	Europe
MPH Sustained Release (SR)	USA, Australia/New Zealand
MPH ER (Methylin)	USA
Methylphenidate Spheroidal Oral Drug Absorption System (MPH-SODAS)	
- Ritalin LA® (Novartis)	USA, Europe, Australia/New Zealand
- Metadate CD™ (UCB)	USA
- Rubifen SR (Novartis)	Australia/New Zealand
Methylphenidate Osmotic Release Oral System (MPH OROS)	
- Concerta® (Janssen)	USA, Canada, Japan, Europe, Taiwan, Australia/New Zealand
- MPH OROS	Central and South America
Dexmethylphenidate (DexMPH) Extended Release (XR)	
- Focalin XR® (Novartis)	USA
MPH Transdermal (MTS)	
- Daytrana® (Noven)	USA
MPH XR suspension	
- Quillivant™ XR (Pfizer)	USA

Medication*	Geographical Location
MPH multilayer release	
- Biphentin	Canada
MTS	Canada
Apo-MPH	Taiwan
3. Short-Acting Amphetamine (AMPH)	
Dextro-AMPH sulfate	
- Dexedrine® (GSK)	USA, Canada
- DextroStat (Wilshire)	USA
Mixed AMPH salts	
- Adderall® (Teva)	USA
Dexamfetamine	
- Attentin® (Medice)	Europe
Dexamphetamine	Australia/New Zealand
4. Longer-Acting AMPH	
Dextro-AMPH sulfate spansules (Dexedrine)	USA, Canada, Australia/New Zealand
Mixed AMPH salts XR	
- Adderall XR (Shire)	USA, Canada
LDX	
- Elvanse	Denmark, Finland, Germany, Liechtenstein, Norway, Spain, Sweden, Switzerland and the United Kingdom
- LDX	Canada, Central and South America
- Tyvense	Ireland
- Venvanse	Brazil
- Vyvanse® (shire)	US, Canada, Mexico and Australia
5. Norepinephrine Reuptake Inhibitor	
Atomoxetine - Strattera	USA, Canada, Central and South America, Europe, Japan, China, India, Taiwan, Australia/New Zealand
6. Short-Acting α-Adrenergic Agonists	
Guanfacine	
- Tenex™ (AH Robins)	USA
- Guanfacine	Canada
Clonidine	Europe, India, Australia/New Zealand
- Catapres	Canada
7. Longer-Acting α-Adrenergic Agonists	
Guanfacine Extended Release (ER)	
- Intuiv® (Shire)	USA
Clonidine Extended Release (ER)	
- Kapvay® (Shionogi)	USA

* We strongly recommend confirming with the respective company website to determine where individual products are marketed and under what specific name.

Table 2Effect sizes for ADHD Medications vs. Other Psychiatric Medications⁶.

Standard Mean Difference	ADHD Medications	Other Psychiatric Medications
0.9+	Amphetamine: ~1.0 (0.91–1.10)	
0.8–0.89		
0.7–0.79	Methylphenidate: ~0.78 (0.64–0.91)	
0.6–0.69	Atomoxetine: 0.65 (0.52–0.82)	
0.5–0.59	Clonidine: 0.58	Second-gen. antipsychotics (SGA)/Haloperidol, Schizophrenia: 0.51–0.53
0.4–0.49	Guanfacine (extended release): ~0.5 (0.43–0.52)	SGA/Mood Stabilizers, Bipolar: 0.40–0.53
0.3–0.39		Selective serotonin reuptake inhibitors, OCD: 0.31–0.41; Antidepressants, MDD: 0.31–0.32

Table 3

Adverse Effects, ADHD Medications

Medication	Common Adverse Effects	Rare Adverse Effects
Methylphenidate Amphetamine	Anorexia, weight loss (12–13%) Insomnia (11–30%) Headaches (12–15%) Abdominal Pain (6–12%) Emotional lability (2–10%)	Tics Dyskinesias Hallucinations Mood dysregulation Rashes Self-injurious ideation Vasculopathy Cardiovascular events
Atomoxetine	Dizziness (6%) Headache (17%) Nausea (20%) Decreased appetite (11%) Weight loss (2%) Constipation (10%) Dry mouth (20%) Insomnia (15%) Fatigue (9%) Sweating (4%) Dysuria/urinary retention (3–7%)	Liver toxicity Seizures (overdoses) Self-injurious ideation Psychosis Mania Mydriasis Rash QT prolongation (blocked hERG channels)
α-adrenergic agonists	Somnolence (38%) Headache (24%) Fatigue (14%) Abdominal pain (10%) Nausea (6%) Lethargy (6%) Irritability (6%) Decreased BP (6%) Decreased appetite (5%) Dry mouth (4%) Constipation (3%)	Orthostatic hypotension Asthenia Chest pain Asthma Increased urinary frequency Enuresis Dyspepsia AV block Bradycardia (17%) Sinus arrhythmia
Bupropion	Irritability Anorexia Insomnia	Tics Seizures
Modafinil	Insomnia Decreased appetite Headaches	Erythema multiforme

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NFC-1 Pharmacokinetic Parameters after Oral Administration of 100 mg in Young and Elderly Participants.

Table 4

Group	Age	C _{max} (µg/ml)	T _{max} (h)	T _{1/2} (h)	AUC _{0-∞} (µg·h/ml)
Young	20 – 32	2.13 ± 0.34	1.3 ± 0.5	4.45 ± 0.72	14.4 ± 3.1
Elderly	68 – 79	3.06 ± 0.69	2.1 ± 1.1	5.17 ± 0.92	24.6 ± 4.4