Classics in Chemical Neuroscience: Methylphenidate

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KEYWORDS: methylphenidate, Ritalin, stimulant, history, hyperkinetic disorder, ADHD,

ABSTRACT: As the first drug to see widespread use for the treatment of ADHD, methylphenidate was the forerunner and catalyst to the modern era of rapidly increasing diagnosis, treatment, and medication development for this condition. During its often controversial history, it has variously elucidated the importance of dopamine signaling in memory and attention, provoked concerns about pharmaceutical cognitive enhancement, driven innovation in controlled-release technologies and enantiospecific therapeutics, and stimulated debate about the impact of pharmaceutical sales techniques on the practice of medicine. In this Review, we will illustrate the history and importance of methylphenidate to ADHD treatment and neuroscience in general, as well as providing key information about its synthesis, structure activity relationship, pharmacological activity, metabolism, manufacturing, FDA-approved indications, and adverse effects.

Background

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that begins in childhood, with an overall prevalence of 1.4-3.0%. Internationally, the largely congruent diagnostic category is termed ‘hyperkinetic disorder’. Under either name, it was historically considered to be a disease exclusive to pediatric and adolescent populations; recently, it has been recognized to persist into adulthood in many individuals. Interestingly, while males are more commonly diagnosed than females in childhood, the reverse is true for adults. Many stepwise treatment guidelines have been published for ADHD; the American Academy of Pediatrics (AAP) guideline is a leading example in the United States. These guidelines generally recommend progression from behavioral interventions only to a combination of behavioral and pharmacologic interventions for elementary-school and adolescent patients. Regarding these pharmacologic interventions, stimulant medications are considered to be the first line treatment – non-stimulant medications are listed as a second-line approach.

This current recommendation is consistent with the modern history of ADHD treatment, as stimulant medications were the earliest class of medications to be broadly efficacious in patients exhibiting hyperactive and inattentive symptoms. Within the stimulant class, methylphenidate (1) has been the drug of choice for almost 50 years; perhaps no other single drug has had such a profound impact on the trajectory of ADHD therapeutics and diagnosis. Despite its already impressive history, 1 is still widely used in both clinical and research settings, and continues to improve our understanding of cognitive neuroscience. This review will give an overview of the history of 1 in the treatment of ADHD and other central nervous system (CNS) disorders, combining several domains of often fragmented information for the “Classics in Chemical Neuroscience” series.
Scheme 1. Original CIBA Synthesis of Methylphenidate (1) by Panizzon from 1944

Chemical Properties and Synthesis

Regarding its essential chemical properties, the molecule commonly known as methylphenidate (1) carries the systematic name methyl-2-phenyl-2-(piperidin-2-yl)acetate, has a molecular formula of C14H15NO2, a molecular mass of 233.31g/mol, a topological polar surface area of 38.3 Å², a cLogP of 2.118 and a melting point of 74 °C. The molecule contains one hydrogen bond donor, three hydrogen bond acceptors, and four rotatable bonds, and fully complies with Lipinski’s rules. The molecule also has two stereocenters that generate four possible configurational isomers. These isomers are customarily divided into two pairs of enantiomers, erythro (2R, 2'S and 2S, 2'S) and threo (2R, 2'S and 2S, 2'R).

The first synthesis of 1 was reported in 1944, using benzyl cyanide (2) and 2-chloropyridine (3) as starting materials (Scheme 1). The first marketed formulations, such as Centedrin, contained a mixture of all four isomers – the separation, interconversion, and preparation of the pure isomers only became a focus after the discovery that the threo isomers were associated with central stimulant effects. Once the (R)-threo isomer was eventually identified as the active species, focused efforts to produce exclusively that isomer began in earnest, culminating in the eventual marketing of dexamfetamine (R-1). Initial approaches to access R-1 focused on the chemical resolution of either critical precursors or of the racemic threo-mixture. Overall, these classical resolution techniques were quite successful, sometimes resulting in successful production of the desired enantiomer on a multi-ton scale. Nevertheless, there was still significant interest in the development of more efficient methods to access chemically pure R-1, including the use of enzymatic approaches toward resolution of the racemic threo mixture. A stereospecific synthetic route to access the racemic threo mixture was first reported by Axten et al. in 1998. Shortly thereafter, two fully enantiospecific syntheses of the (R)-threo conformation were independently reported, along with a fully enantioselective synthesis of the (S)-erythro isomer. These Prashad et al. (Novartis) syntheses used an asymmetric aldol condensation as their key transformation, but a number of other chemically creative methods have been subsequently reported to generate enantiomerically pure material: rhodium-mediated CH insertion, stereoselective Evans imide coupling, intramolecular Michael addition, and asymmetric ketone reduction. Although not all of these approaches are suitable for use in process chemistry, they have often been essential for the development of novel analogues of 1.

Manufacturing Information

CIBA pharmaceuticals filed the original patent for preparation of 1 in 1950; they subsequently filed a method of use patent on 1 (under the brand name Ritalin) to treat psychiatric disorders in 1954. Due to subsequent patent expiration, 1 is now available through many different manufacturers in a wide range of formulations.

An immediate release (IR) oral tablet continues to be available under the brand name Ritalin (Novartis), and many AB-rated bioequivalent generic IR tablets are also available. Ritalin-SR (Novartis), Concerta (Janssen), Methylin ER (Mallinckrodt), and Metadate ER (UCB) are available as extended release (ER) tablet formulations. Quillichew ER (Pfizer) is a chewable ER tablet (CET) formulation – an IR chewable tablet (CT) is also available from Novel Labs. ER capsules include Ritalin LA (Novartis), Metadate CD (UCB), and Aptsensio XR (Rhodes Pharm). In addition to these products, other tablets and capsules have previously been available, but their manufacture has since been discontinued by their parent companies.
For individuals who are unable to swallow tablets or capsules, oral solutions (S) are sold under the brand name Methylin (Mallinckrodt) or as several AB generics; there is also an ER oral suspension (ES), Quillivant XR (Nextwave), and an ER transdermal patch (P), Daytrana (Noven) (Figure 1).

Intellectual properties and patents regarding the production and use of the pure R-1 enantiomer were granted to Novartis in the year 2000. The compound R-1 is available through Novartis as both the IR tablet, Focalin, and as an ER capsule, Focalin XR; both of these enantiopure products also have several AB generic competitors. While market fragmentation has caused the relative share of profits for the most popular products to decrease over time, in aggregate the annual sales of pharmaceutical products containing 1 continue to be very strong and have been estimated at $1-1.3 billion over the past several years.

A notable manufacturing issue has recently arisen regarding the proliferation of the many ER products containing 1. In contrast to other ER tablets, the Concerta product uses a proprietary osmotic release oral-delivery system (OROS). Of these generics, the Actavis product was the only one to receive an AB rating, as this product is actually manufactured by Janssen and licensed to Actavis as the authorized Concerta generic. In contrast, the Mallinckrodt and Kudco products were given a BX rating in November 2014 after they were found to have a slower rate of drug delivery than OROS; this rating resulted in the United States Food and Drug Administration (FDA) releasing a statement that “the Mallinckrodt and Kudco products are still approved and can be prescribed, but are no longer recommended as automatically substitutable at the pharmacy (or by a pharmacist) for Concerta.”

The FDA further established that these generic manufacturers should either provide additional data within 6 months that directly compares the release profiles of their products to Concerta or voluntarily remove their products from the market. While negotiations regarding this ruling are still ongoing, the FDA guidance on this topic has nevertheless become a topic of general interest in the pharmaceutical industry given the increasing proliferation of sophisticated drug delivery methods, the age of the standard guidelines underlying bioequivalence, and the relative lack of data transparency regarding these bioequivalence studies.

Pharmacokinetics and Drug Metabolism

Following oral administration in humans, 1 has a reported absolute bioavailability (F) between 0.11-0.53, indicating pre-systemic elimination of the drug. This finding is well aligned with results from monkeys (F = 0.22) and rats (F = 0.19). Peak concentration (C_max) is achieved after approximately two hours for IR formulations; the plasma half-life (t_1/2) is also about two hours. These values do not differ substantially between children and adults. Likewise, ingestion of food prior to dosing does not appear to alter pharmaco-
kinetics substantially, though absorption can be either accelerated or slowed, partially depending on the fat content of the meal.$^{15,37,38}$

The various ER formulations available have distinct absorption kinetics from both IR formulations and from each other; Metadate CD and Ritalin LA mimic twice daily (BID) dosing, while Concerta mimics three-times daily (TID) dosing.$^{32,39,40}$ However, despite the well-known pharmacokinetic parameters of these various formulations, the selection of an appropriate drug product and dosing regimen to maximize benefit and minimize side effects remains largely a matter of applied clinical expertise for each individual patient.

Genetic studies have identified polymorphisms in the dopamine transporter (DAT) and other CNS proteins (including GABRA2, SLC6A3, CES1, COMT and 5-HTTLPR) that appear to correlate with the likelihood of developing various side effects or therapeutic responses, highlighting the complex biological milieu that underlies the need for such an individualized approach.$^{41–47}$

Metabolism of 1 occurs primarily via de-esterification by carboxylesterase 1A1 (CES1A1) to form ritalinic acid (8), with between 60-80% of the dose excreted as this metabolite (Figure 2). Intriguingly, this metabolism proceeds in a stereoselective manner across several species, resulting in a preponderance of R-1 in systemic circulation.$^{48,49}$ This effect is especially pronounced during first-pass metabolism, with a 10-40 fold lower CES1A1 catalytic efficiency for R-1 as compared to S-1.$^{50}$ A similar enantiomeric preference has been reported for the formation of the active metabolite ethylphenidate (9) via transesterification when 1 is co-administered with ethanol.$^{51,52}$

The formation of several hydroxylated metabolites (10 – 12) has also been reported in multiple species, although they are less abundant than 8.$^{53}$ These oxidative metabolites have been demonstrated to retain some pharmacologic activity, with para-hydroxymethylphenidate (11) reportedly increasing locomotor activity to a significantly greater degree than 1 itself.$^{54}$

**Pharmacology**

The primary pharmacological targets for 1 are DAT and the norepinephrine transporter (NET).$^{55–57}$ Blockade of these neurotransmitter transporters results in decreased presynaptic re-uptake following release and increased average neurotransmitter concentrations in the synaptic cleft.$^{58,59}$

According to standardized data generated by the Psychoactive Drug Screening Program (PDSP) the affinity of 1 for human DAT is nearly 10-fold higher than for NET (Table 1). Additional competition binding experiments have shown no activity for 1 below 10 µM at the human serotonin transporter (SERT), any of the serotonin receptors, or any muscarinic or nicotinic acetylcholine receptors. However, binding to several alpha 2 adrenergic receptor (α2) subtypes has been observed, which may contribute to its efficacy – these targets are shared by non-stimulant compounds also approved for use in ADHD.$^{60}$

To identify these pharmacological targets, early studies were crucial in noting the ability of 1 to alter CNS catecholamine metabolism and decrease dopamine (DA) uptake.$^{61–63}$

**Table 1. Pharmacological profile of methylphenidate (1).**

<table>
<thead>
<tr>
<th>Receptor/Transporter</th>
<th>Kᵢ(µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine Transporter (DAT)</td>
<td>0.041</td>
</tr>
<tr>
<td>Norepinephrine Transporter (NET)</td>
<td>0.345</td>
</tr>
<tr>
<td>Alpha 2A Adrenoceptor (α₂A)</td>
<td>5.600</td>
</tr>
<tr>
<td>Alpha 2B Adrenoceptor (α₂B)</td>
<td>2.420</td>
</tr>
<tr>
<td>Alpha 2C Adrenoceptor (α₂C)</td>
<td>0.860</td>
</tr>
</tbody>
</table>
While subsequent investigations yielded increasingly detailed information about the blockade of DAT and NET by 1, it would take several decades before these molecular mechanisms could be associated with functional changes in CNS activity. Indeed, studying the connection between neurotransmitter reuptake blockade and circuit- or regional-level changes in activity is currently a highly active area of research.

In the context of bridging this knowledge gap, the generation of an \(^{11}\text{C-R-threo}\)-methylphenidate (\(^{11}\text{C-R-1}\)) PET tracer was a crucial development. Application of this tool revealed that context-dependent amplification of DA signals in the basal ganglia can enhance task-specific neuronal signaling and increase the saliency of task at hand. Interestingly, these effects appear somewhat dependent on basal DA tone, providing another possible explanation for dramatic inter-individual variability seen in response to 1.

The later application of a different PET tracer, \(^{99}\text{Tc-TRODAT-1}\), revealed that adults with ADHD had higher expression of DAT than healthy controls, and that elevated striatal DAT was a potential prognostic predictor for improved responses to 1, further supporting the impact of basal DA signaling capacity on its efficacy. In addition to causing task-dependent alterations in the functional connectivity of brain regions crucial for attention and information processing, 1 also has a significant impact on such connectivity in the resting brain – effects in both contexts are thought to contribute to its ability to help differentiate signal from noise, focus attention, and restore goal-directed behavior in ADHD.

Alongside efforts to identify the pharmacological target(s) of 1, complementary studies were underway to determine the specific enantiomer responsible for its activity. \(^{11}\text{C-1}\) PET tracers proved to be essential in this line of research as well. Specifically, \(^{11}\text{C-R-1}\) exhibited reproducible and saturable uptake into human and baboon brain, where it was found to be preferentially localized in the basal ganglia and striatal regions, while the opposite enantiomer exhibited only diffuse and non-specific binding. Pre-clinical behavioral studies with chirally-resolved material later demonstrated enhanced activity of \(R-1\) as compared to the \(\text{threo}\) racemate. Eventually, comparisons of purified \(R-1\) to the racemic \(\text{threo}\)-mixture demonstrated similar efficacy with lower total dosages in both children and adults with ADHD, confirming it as the active enantiomer \textit{in vivo}.

### Structure Activity Relationship

To further improve understanding of the structure-activity relationship (SAR) underlying the effects of 1, many groups went on to synthesize novel derivatives of this compound. Some of the earliest efforts in this area were not strictly focused on 1 alone, but were broadly developing the phenylisopropylamine class of compounds; this area of research continues to be highly relevant today, given the large number of synthetic stimulants and hallucinogens that have been generated from this structural motif.

More explicit explorations of the scaffold of 1 focused on modifying specific areas of the molecule, often the phenyl ring or the ester. Other efforts systematically introduced specific functional groups, such as halides. Once it became apparent that the differential conformations of the \(\text{erythro}\)- and \(\text{threo}\)-isomer pairs conferred differing activity, later studies focused on the generation of conformationally-locked analogues to mimic the presumed hydrogen bonding interactions between the amine and carboxyl groups occurring in the \(\text{threo}\)-isomers. Although they were not necessarily direct studies of analogue pharmacology, the analysis of hydroxylated metabolite activity and the use of the scaffold of 1 as an advanced intermediate to access other compound classes both contributed significant information for better understanding the SAR of this family of structures.

A quantitative SAR analysis of 80 \(\text{threo-1}\) analogues recently reported findings in agreement with these previous SAR studies: large ortho-groups are poorly tolerated, as are bulky substitutions that project above or below the plane of the phenyl ring; electron withdrawing groups (EWG) at the meta- or para- positions lying within the plane of the ring are useful for increasing DAT affinity; substitutions off of the piperidinyl nitrogen are poorly tolerated; and decreasing polarity near the carboxyl moiety correlates with decreasing DAT inhibition.\(^{84,87,91}\)
Figure 3. Key SAR features for 1 that increase the affinity of analogues for DAT.

Adverse Effects and Dosage

As a stimulant compound, 1 has many of the general side effects often associated with this class of medications, including appetite loss, dry mouth, anxiety, nausea, insomnia, restlessness, dyskinesia, dizziness, dry eye, and hyperhidrosis; 1 is pregnancy category C, meaning that risk cannot be ruled out if taken during pregnancy or while breastfeeding. 92

Pharmaceutical products containing 1 also carry several warnings regarding uncommon, but serious, adverse effects associated with their use, including the emergence or potentiation of psychotic or manic symptoms, long-term growth suppression, seizures, priapism, peripheral vasculopathy, blurred vision, and risk of sudden death in individuals with preexisting structural cardiac abnormalities. 92-96 Due to ongoing questions about the prevalence of these potentially serious side effects in children and adolescents, a large-scale pharmacovigilance program (known as ADDUCE) is currently underway in Europe. 97

Like nearly all stimulant compounds, 1 carries with it a risk of addiction. 98 In 1971, the Drug Enforcement Administration (DEA) placed it into Schedule II, the most restrictive category for compounds with a known medical use. 99 Because of this high risk, all products containing 1 have a black box warning concerning drug dependence.

The non-medical use of prescription stimulants by both adolescents and adults has been repeatedly demonstrated, though the reported incidence of such abuse appears to vary from 5-35%, depending on the methods used and the exact population studied. 95 The peak risk age for starting such abuse is estimated to be between 16-19 years, with a new user rate of 0.7-0.8% per year. 100 Furthermore, the age to first medical or non-medical use of prescription stimulants has decreased over the last 15 years, which has frequently been associated with an increase in prescriptions for these substances. 101,102 However, not all abuse metrics can be simply attributed to this increase, and the non-medical use of 1 in particular has been reported to be declining in adolescents. 103 Significant concerns about this issue remain, especially for some particularly vulnerable populations. Notably, there is an increased prevalence of 1 abuse amongst individuals with a prior history of IV substance use; the health risks of such abuse are likely increased when combined with other abused drugs. 104-106

Although switching to a different stimulant compound due to side effects from 1 may be necessary in some individuals, management of these issues is often approached through careful dose titration, medication scheduling, and use of drug holidays. 107,108 It is worth noting that such strategies are necessarily a balancing act between competing concerns. While some of the most commonly reported side effects, such as insomnia and reduced appetite, are often combated by using IR formulations, there is evidence to suggest that the abuse potential of ER formulations is lower. 109 Furthermore, such a switch can have economic consequences – ER formulations are generally more expensive on a per-unit basis, although they can be less expensive over the long-term for individuals where compliance is a factor in sub-optimal treatment. 110

Regardless of the formulation chosen, most products containing 1 have a wide range of acceptable dosages and individualization is often necessary (Table 2). Intriguingly, recent results have indicated that patient weight may be a reasonable clinical guide to dosing, with 1 mg/kg as the median efficacious dose in pediatric, adolescent, and adult populations. 111

Indications

1 is approved by the FDA for the treatment of ADHD in individuals older than 6 years of age and younger than 65 years of age, based on demonstrated efficacy across many clinical trials. 112-115
Through the 1950’s and 1960’s the stimulant compound 1 more often found use in depression, narcolepsy, lethargy, and barbiturate overdose; the trade name Ritalin was actually derived from Leandro Panizzon’s nickname for his wife, “Rita”, who used the compound to elevate her blood pressure while playing tennis.\textsuperscript{124}

The present-day inversion of the frequency of these various therapeutic uses for 1 occurred only gradually. During this interim period, before ADHD came to dominate its identity, 1 was already being used as a tool to understand the molecular biology of other psychiatric illnesses, notably implicating excess dopaminergic tone as a contributing factor to schizophrenia, and helping to elucidate the role of synaptic dopamine release in stimulant abuse and addiction.\textsuperscript{129,130}

During the 1970’s and 1980’s, more research began to be conducted in the application of stimulants to hyperactive children, often using 1 as a basis for their positive findings.\textsuperscript{131} As the interest in diagnostic recognition of ADHD grew, so did the global consumption of stimulant drugs.\textsuperscript{132–136} Among such compounds, 1 was regarded early on as the drug of first choice, and for decades it had a near monopoly on the market for treatment of ADHD.\textsuperscript{131}

By the turn of the twenty-first century, recognition was no longer a problem for ADHD, and 1 no longer exclusively controlled the ADHD market. In the 1990’s and 2000’s, 1 was increasingly reformulated in an effort to retain market share as multiple alternative ADHD drugs (13–18) came on the market (Chart 1). Indeed, 1 is one of only a handful drugs thus far that have employed the contentious ‘chiral switch’ strategy, where a racemic product on the market is rebranded as the enantiomerically pure version, frequently without head-to-head efficacy or safety comparisons of the two drugs.\textsuperscript{137,138}

As the profits and portfolios associated with ADHD drugs expanded dramatically, media reports had begun to focus on the possibility of over-diagnosis of this disorder; such controversies seemingly only increased the persistence of ADHD into adulthood was recognized and the

### Table 2. Generalized dosing chart for different formulations of 1.\textsuperscript{*}

<table>
<thead>
<tr>
<th>Formulation Type</th>
<th>Starting Dose (mg)</th>
<th>Titration Increment (mg/week)</th>
<th>Max. Daily Dose (mg)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR Tablets / Capsules</td>
<td>5</td>
<td>5 - 10</td>
<td>60</td>
<td>BID - TID</td>
</tr>
<tr>
<td>IR Oral Solution</td>
<td>5</td>
<td>5 - 10</td>
<td>60</td>
<td>BID -TID</td>
</tr>
<tr>
<td>ER Tablets / Capsules</td>
<td>20</td>
<td>20</td>
<td>60</td>
<td>QD</td>
</tr>
<tr>
<td>OROS ER Tablets</td>
<td>18</td>
<td>18</td>
<td>54 (6-12 y) 72 (12+ y)</td>
<td>QD</td>
</tr>
<tr>
<td>ER Oral Suspension</td>
<td>20</td>
<td>10 - 20</td>
<td>60</td>
<td>QD</td>
</tr>
<tr>
<td>Transdermal Patch</td>
<td>10</td>
<td>5; 5; 10</td>
<td>30</td>
<td>9 h ON; 15 h OFF</td>
</tr>
</tbody>
</table>

*Consult the approved package insert when dosing a specific product.

In addition to this FDA-approved indication, 1 has a lengthy history in other, off-label uses. Some of the most actively researched uses include treatment of lethargy in cancer patients, stuttering, cocaine addiction, methamphetamine addiction, major depressive disorder, mental fatigue following traumatic brain injury, and narcolepsy.\textsuperscript{116–123}

### History and Importance in Neuroscience

For much of modern medical history, ADHD was a disorder that struggled for recognition.\textsuperscript{124} Although Sir Alexander Crichton had described a condition with striking similarities to ADHD as early as 1798, the disorder was not recognized under its current name until the publication of the DSM-III-R in 1987.\textsuperscript{125,126} In between those periods, several other individuals had identified cohorts of hyperkinetic children, particularly George F Sill in the 1900’s; however, in the mid-twentieth century United States, ADHD was a relatively minor area of study, being conceptualized by some as a type of minimal brain damage.\textsuperscript{127,128} Seminal work by Charles Bradley in the late 1930’s had already demonstrated success in treating hyperkinetic children with the stimulant benzedrine, though the importance of this finding was not yet widely appreciated.\textsuperscript{6} Likewise, although 1 was first synthesized by Leandro Panizzon only shortly thereafter, its utility in the context of childhood hyperactivity was not immediately recognized.
number of stimulant prescriptions for adults with an ADHD diagnosis began to rise at a rate even faster than it initially had for children. Several studies have since indicated that ADHD is not being over-diagnosed by using rates of false positives or comparing population estimates of prevalence to the pool of diagnosed individuals. However, these studies do not directly address the implicit question of whether the actual diagnostic criteria being used for such estimates are themselves inappropriate or vague. While such philosophical dilemmas have always attended psychiatric disorders, it is worth noting that the difficulty of obtaining a diagnosis for a syndrome without a single diagnostic test is at least explicitly acknowledged in the package insert for products containing I.

Enterling the 2010’s, this controversy had a significant and positive impact on the proliferation of research looking for genetic and functional markers that can be accurately used for the diagnosis of ADHD and other neurodevelopmental disorders. Perhaps, if given enough time, the identification of unambiguous biomarkers of neuropsychiatric disorders will finally lay these age-old diagnostic difficulties to rest.

Until then, efforts are underway to identify biomarkers that can at least predict the likelihood of an efficacious response to I. This research should help optimize future prescribing patterns, and has already yielded much important information regarding how stimulants affect overall brain function. Other studies with I have also played a large role in more specifically defining how alterations in dopaminergic signaling can affect attention and memory. Examinations of the effects of I in individuals with and without ADHD have recently begun to unravel the complex issue of how baseline capacity and prior experience interact with stimulant use to generate either working memory improvements or impairments in specific contexts.

Such nuanced understanding will likely be essential to truly improve our grasp of ADHD etiology and to inform and understand the growing use of I and other stimulant compounds as ‘cognitive enhancers’ or ‘smart drugs’. While the efficacy of such enhancement attempts is still very much in question, individuals across numerous sectors of society have nevertheless been reported to use them – from students to economists, from surgeons to professional video gamers.

So once again I has found itself as a foot-soldier at the forefront of an ethical and philosophical battle (e.g. Is pharmacological enhancement permissible for ‘normally functioning’ individuals? If so, under what circumstances? If not, why is it different than other widely accepted behavioral strategies for enhancing learning and memory?). Fortunately, in this conflict, it will not be alone. Many relatively common neuropsychiatric disorders like depression, Alzheimer’s disease, and schizophrenia have cognitive deficits as a component, as the number of new mechanisms and compounds tested to address these issues has rapidly proliferated, so has their assessment in healthy individuals.

Over its 70-plus year history, I has been a stimulant catch-all, a driver for diagnostic recognition, a market-leader, a rebranding poster-child, and a flashpoint for controversy. It has illuminated the essential functions of catecholamine neurotransmitters and pushed the boundaries of cognitive neuroscience. Above all, it has been an enormously successful therapeutic for the treatment of...
a once marginalized disorder. Extricating the history of ADHD from the history of I is a nearly impossible task – the difficulty in accurately assessing how much the successes of the one drove the growth of the other is a testament to how significant an impact it truly has made (Figure 4).

The compound I has impacted not only the pursuit of medical and neuroscientific knowledge, but has also helped shape the culture of long-term brand management and direct-to-consumer advertising within the pharmaceutical industry, and has found its way into the attention of the media and the imagination of popular culture. For all of these reasons and more, I is a true classic in chemical neuroscience… that hasn’t yet given up providing noteworthy modern twists.

Figure 4. PubMed manuscripts referencing “attention deficit hyperactivity disorder” or “hyperkinetic disorder (blue). DEA yearly production quotas for I (black).

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ABBREVIATIONS

ADHD, attention deficit hyperactivity disorder; FDA, United States Food and Drug Administration; CNS, central nervous system; DAT, dopamine transporter; NET, norepinephrine transporter; DEA, Drug Enforcement Administration; ER, extended release; IR, immediate release; EWG, electron withdrawing group; SAR, structure-activity relationship; QD, daily; BID, twice daily; TID, three times daily.

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Arzneimittel-Forschung, 12, 902–907.


Figure 1. Timeline showing the FDA approval dates for the various formulations of methylphenidate (1). * = Enantiopure formulation. The brand names of the initial entries for each class of products are listed above the appropriate timeline. Branded products are shown in red. The first fully ‘generic’ approval for each formulation is shown in white, with a subse-quent arrow to indicate ongoing approvals for additional generic manufacturers.

189x64mm (150 x 150 DPI)
Figure 2. Known metabolites of 1. The primary route of clearance forms 8 (blue). Transesterification to 9 occurs in the presence of ethanol (red). Oxidative transformations (dashed arrows) are presumed to occur via the activity of several CYP450 enzyme family members.
Figure 3. Key SAR features for 1 that increase the affinity of analogues for DAT.

42x36mm (300 x 300 DPI)
Figure 4. PubMed manuscripts referencing "attention deficit hyperactivity disorder" or "hyperkinetic disorder" (blue). DEA yearly production quotas for methylphenidate (black).

Figure 4
250x152mm (300 x 300 DPI)
Chart 1. Structures of other FDA-approved compounds for the treatment of ADHD as of June 2016. Stimulants are labeled in red, non-stimulants are labeled in black.

Amphetamine 13  Lisdexamfetamine 14  Methamphetamine 15
Atomoxetine 16  Clonidine 17  Guantacine 18
Scheme 1. Original CIBA Synthesis of Methylphenidate (1) by Panizzon from 1944