

# Prescription Stimulant-Induced Neurotoxicity: Mechanisms, outcomes, and relevance to ADHD


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Attention-deficit/hyperactivity disorder (ADHD) is a relatively prevalent neuropsychiatric and neurodevelopmental condition characterized in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* as difficulty sustaining attention and maintaining tasks at hand, heightened distractibility, and other deficits in executive functioning. Prescription stimulants—amphetamine (AMP) and methylphenidate (MPH)—are the first-line treatment(s) for ADHD in both pediatric and adult populations and exist in many formulations. Troublingly, the non-medical use (NMU) of amphetamine and methylphenidate is more prevalent in the American population, especially on college and university campuses, than the condition of interest. The neurotoxicological profile and NMU epidemiology of prescription stimulants is of direct relevance to primary care physicians and psychiatrists as they are the providers most frequently tasked with the treatment of ADHD and the surveillance of substance misuse behaviors in the young adult population. As comprehensive literature reviews of the mechanisms and potential adverse sequelae of prescription stimulant-induced neurotoxicity intended for medical clinicians have been quite sparse in the last decade—especially given the gravity of the issue—this article includes a brief primer on ADHD etiology and pathophysiology; considers the current state of NMU epidemiology; reviews the mechanisms of action of AMP and MPH; and, finally, summarizes known molecular and clinical manifestations of AMP and MPH neurotoxicity.

## Keywords

attention deficit disorder with hyperactivity • prefrontal cortex • amphetamine • central nervous system stimulants • students • young adults • prescription drug misuse

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## Introduction

The clinical utility of prescription stimulants for the treatment of attention-deficit/hyperactivity disorder (ADHD) is well characterized and robust.<sup>1</sup> ADHD is a persistent and pervasive neurodevelopmental disorder with an etiology influenced by the interplay of environmental and genetic factors.<sup>2</sup> The cardinal symptoms of ADHD—hyperactivity, impulsivity, and/or inattention—are usually noticed by parents, teachers, and/or other caregivers in mid- to late childhood. Symptoms may cause noticeable impairments in social interaction and limit effective communication, social cooperation, and academic success.<sup>3,4</sup> Early diagnosis by qualified mental health professionals (eg, psychotherapists, psychiatrists, behavioral neurologists) is associated with greater long-term symptom management.<sup>5</sup> Interestingly, up to 85% of patients diagnosed with ADHD early in life continue to have symptoms into adulthood, meaning long-term treatment consideration is likely necessary.<sup>6–9</sup> Amphetamine (AMP) salts and methylphenidate (MPH), both prescription stimulants with many formulations (Table 1), have been recommended as first-line treatments for ADHD in both pediatric and adult populations in the

**Table 1.** FDA-Approved Formulations for the Treatment of ADHD

Trade name	Dosage	Maximum recommended
<i>Methylphenidate</i>		
Focalin XR	5–40 mg capsules	1 mg/kg or 30 mg/day
Concerta	18–54 mg tablets	2 mg/kg or 72 mg/day
Ritalin LA	10–40 mg capsules	2 mg/kg or 60 mg/day
Metadate CD	10–60 mg capsules	2 mg/kg or 60 mg/day
Daytrana	10–30 mg patches	30 mg/day
Ritalin SR	20 mg tablets	2 mg/kg or 60 mg/day
Methylin ER	10–20 mg tablets	2 mg/kg or 60 mg/day
Quillivant	25 mg/5 mL suspension	60 mg QAM
Focalin	2.5–10 mg tablets	2 mg/kg or 60 mg/day
Ritalin	5–20 mg tablets	2 mg/kg or 60 mg/day
Methylin	5–20 mg tablets or 5–10 mg/5 mL solution	2 mg/kg or 60 mg/day
<i>Amphetamine</i>		
Vyvanse	10–70 mg capsules	1 mg/kg or 70 mg/day
Adderall XR	5–30 mg capsules	1 mg/kg or 30 mg/day
Dexedrine	5–15 mg capsules	1 mg/kg or 30 mg/day
Adderall	5, 7.5, 10, 12.5, 15, 20, 30 mg tablets	1 mg/kg or 30 mg/day
Dextroamphetamine	5–10 mg tablets	1 mg/kg or 30 mg/day
ProCentra	5 mg/5 mL solution	1 mg/kg or 30 mg/day

United States for decades, although adjunctive behavioral therapy may produce even better outcomes in adults.<sup>1,5-7,10-14</sup>

Although the employment of stimulants in the treatment of nosologic predecessors to ADHD has been commonplace since the mid-20th century,<sup>8,15</sup> adequate comprehensive consideration of the potential neurological sequelae of long-term stimulant use, prescribed or otherwise, is noticeably lacking in the literature. Alarming, the Schedule II status of stimulant medications indicates their abuse and dependency potential is similar to the medications implicated in the current opioid epidemic. These factors should be of great importance to the interested clinical, toxicological, and epidemiological communities given the popular ease of access to, high prevalence of, and largely unknown long-term neurological sequelae of prescription stimulant use and misuse that I consider in this article. Importantly, the prevalence of ADHD is estimated to be between 5% and 10% in American children and 2.8% and 5.2% in adults, yet the prevalence of non-medical use (NMU) of stimulants is estimated to exceed that of the very condition(s) for which they are indicated.<sup>10,11,16-20</sup> If prescription stimulants are more prevalent among the population than the condition(s) they are prescribed for, clinicians and epidemiologists should know what to look for when future patients without documented ADHD present with symptoms of dopaminergic and noradrenergic pathology. The same is true for those with a history of ADHD treatment, although historical stimulant use would hopefully be documented. Similar to medications approved for any variety of condition, NMU of stimulants indicated for ADHD is associated with a variety of adverse effects, and the potential for serious harm in

**Table 2.** *DSM-5* Diagnostic Criteria for ADHD by Presentation

<b>Presentation</b>	<b><i>DSM-5</i> diagnostic criteria (≥ 5 of the following for at least 6 months in adults)</b>
Predominantly inattentive	<ul style="list-style-type: none"> <li>• Frequent failure to pay attention to detail in work, academic, or social settings</li> <li>• Difficulty sustaining attention in tasks or play activities</li> <li>• Frequently fails to listen when spoken to directly</li> <li>• Difficulty managing and organizing tasks and activities</li> <li>• Tends to avoid tasks requiring sustained mental effort</li> <li>• Frequently loses materials necessary for daily tasks</li> <li>• Easily distracted by extraneous stimuli</li> <li>• Often forgetful of daily activities</li> </ul>
Combined	<ul style="list-style-type: none"> <li>• Shows characteristics of inattentive <b>and</b> hyperactive/impulsive presentations</li> </ul>
Predominantly hyperactive/impulsive	<ul style="list-style-type: none"> <li>• Frequent fidgeting, tapping, or squirming</li> <li>• Often leaves task at hand when attention is expected</li> <li>• Often restless</li> <li>• Struggles to play or engage in restful activities</li> <li>• Seems to be constantly moving or unable to sit still for extended periods of time</li> <li>• Talks more than expected</li> <li>• Tends to blurt out answers before question is finished</li> <li>• Often interrupts others</li> <li>• Has trouble waiting in line</li> </ul>

the long term remains poorly characterized.<sup>21</sup> This article includes a brief primer on ADHD etiology and pathophysiology; considers the current state of NMU epidemiology; reviews the mechanisms of action of AMP and MPH; and, finally, summarizes known molecular and clinical manifestations of AMP and MPH neurotoxicity.

## Primer on ADHD Etiology and Pathophysiology

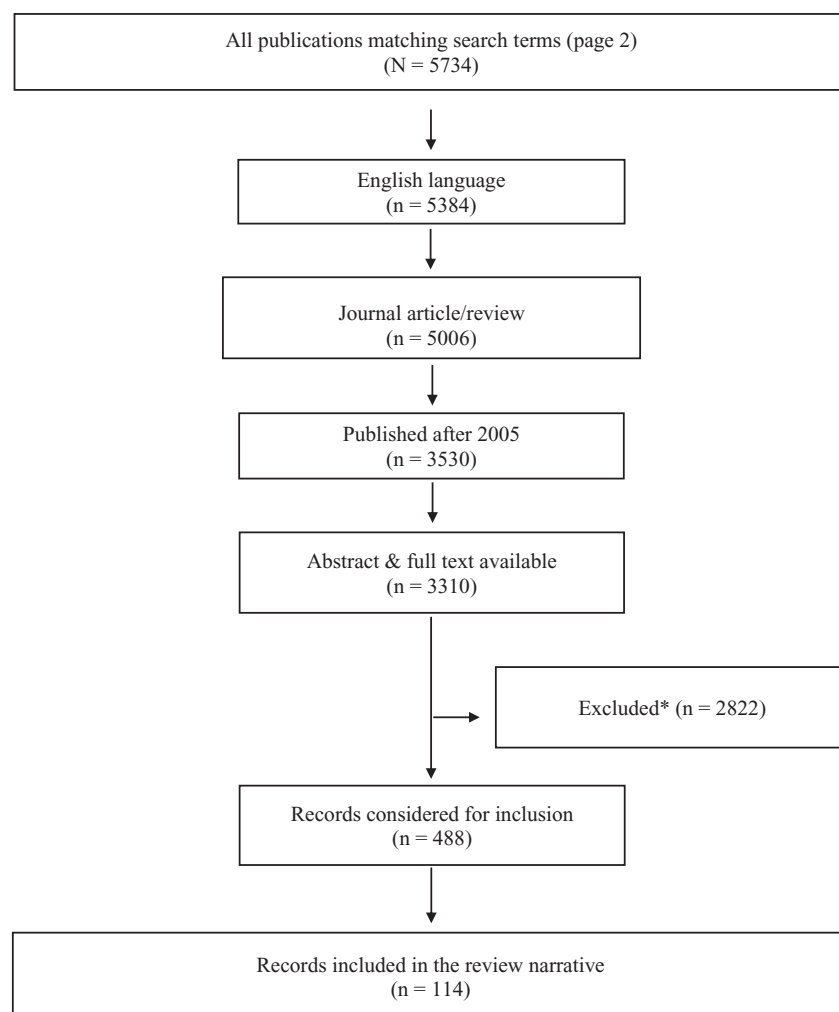
ADHD (previously called attention-deficit disorder) is characterized by pervasive cognitive, behavioral, and emotional dysfunction.<sup>4,22</sup> There are three clinical presentations of ADHD classified in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; Table 2)*, with the combined presentation being the most prevalent (62%).<sup>23</sup> Although roughly 75% of the risk for ADHD is attributed to genetics, large genome-wide association studies have been mostly unsuccessful in convincingly detecting DNA polymorphisms specifically associated with ADHD.<sup>2,20,24</sup> Thankfully, this may be changing as recent work has found variants on *FOXP2*, *SORCS3*, and *DUSP6*, among other genes, to be associated with a 1.077 to 1.198 increased odds of ADHD development.<sup>25</sup> Variants of genes involved in dopamine transmission, *DRD4*, *DRD5*, *COMT*, and *DAT1*, among others, have been shown to be associated with ADHD, providing evidence for the catecholamine dysregulation hypothesis of ADHD.<sup>2,24,26–31</sup> Norepinephrine (NE) signaling is believed to be attenuated alongside dopamine (DA) in ADHD, which is likely the reason the NE reuptake inhibitor atomoxetine alleviates ADHD symptoms in some with the condition.<sup>27,32–34</sup> Inhibition of neurotransmitter transporters, a mechanism of action of both AMP and MPH, prevents presynaptic reuptake of DA and NE molecules, thus allowing postsynaptic receptors greater access to their respective ligands.<sup>35–37</sup> The greater effectiveness of AMP and MPH compared to atomoxetine in individuals with ADHD is likely due to the frequent functional and anatomical changes seen in dopamine transport (DAT) in dopaminergic regions such as the frontal cortex, striatum, and basal ganglia compared to noradrenergic regions.<sup>1,38–42</sup> Serotonergic, acetylcholinergic, opioid, and glutamatergic signaling pathways are implicated in the pathophysiology of ADHD, as well, but current pharmacotherapeutic options target mainly NE and DA.<sup>43,44</sup> As the etiology of ADHD is not unitary, it is likely that causal pathways will be interactive and dynamic; genetic, structural, functional, environmental, and social factors each appear to contribute to ADHD pathophysiology.<sup>45</sup> Importantly, though the mechanisms of action of stimulants are identical in those with and without ADHD, their known outcomes are not.<sup>18,42,46</sup>

## Methods

PubMed was used to search the literature for English-language articles published between 2005 and April 2020. The cutoff year of 2005 was selected as the novel Adult ADHD Self-Report Scale, version 1.1, the first adequate instrument used in the assessment of adult ADHD symptomatology, entered use in the World Health Organization's World Mental Health Survey Initiative that year.<sup>47</sup> Search terms including *ADHD*, *attention deficit hyperactivity disorder*, *amphetamine*, and *methylphenidate* were used alone and in combination with *toxicity*, *epidemiology*, *adverse effects*, *etiology*, *pharmacology*, and/or *misuse*. The additional filters of *journal article* and *review* were used to identify peer-reviewed articles addressing amphetamine and/or methylphenidate toxicology, misuse, and pharmacology, as well as ADHD treatment, etiology, pathophysiology, and epidemiology. The reference lists of retrieved articles were regularly hand-searched for other relevant reviews, trials, or original research to identify additional records for use. Titles, abstracts, and full texts that resulted from keyword searches were reviewed briefly to

determine topical relevance, and the journal an article was published in was checked for quality using InCites Journal Citation Reports and/or Google Scholar Metrics. Individual articles were rated for quality using the McMaster University Effective Public Health Practice Project tool when deemed appropriate.<sup>48</sup> To reduce the number of publications to review, the most up-to-date review papers were used whenever possible. Publications were selected according to professional judgment of quality, relevance to MPH/AMP toxicology or pharmacology, and whether findings had clinical relevance. Older publications, such as a 1981 report on MPH hallucinosis, were included when necessary.<sup>49</sup>

Exclusion of an article occurred if (1) it pertained to ADHD comorbid with a diagnosed psychiatric or developmental disorder (eg, autism spectrum disorder, obsessive-compulsive disorder, mood disorder), (2) concerned the effectiveness of ADHD interventions used outside mainstream medicine (eg, fish oil, ginger), (3) pertained to toxicity profiles beside neurological, (4) focused on psychosocial management of ADHD, or (5) concerned ADHD secondary to some other medical condition. The PRISMA flow diagram for this review's selection procedure is presented in Figure 1.<sup>50</sup> After applying inclusion and exclusion criteria and hand-searching reference lists from important articles in the literature, a total of 488 articles were considered for review. Of the 5006 articles initially yielded during the search, 114 were used in authoring this article.



**Figure 1.** Flow Diagram of Records Identified, Screened, and Included.

\*Excluded due to topical irrelevance, low publication quality, or publication type

## Non-Medical Use Epidemiology

Recognition by the psychiatric and behavioral medicine communities that ADHD persists into adulthood in at least a large proportion of cases has increased subsequent availability of stimulant medications in the adult population.<sup>51</sup> Given the strong motivation by young adults (aged 18 to 25 years)—many of whom are in college—to perform well academically, the positive effects on cognitive functioning in those who use stimulants for ADHD are plausibly expected to produce similar effects in anyone who uses them. As stimulant medications are known to boost working memory, processing speed, sociability, attention, etc in patients with ADHD, the average individual engaging in NMU simply (and erroneously) expects those clinical benefits to translate into improved test scores, more hours spent studying, and cognitive stamina.<sup>26</sup>

Misuse of stimulants, defined as the NMU of prescription medications used to treat ADHD and other conditions, is especially prevalent on American college campuses.<sup>52</sup> American young adults misuse prescription stimulants significantly more frequently each year compared to the general adult population.<sup>19,53–55</sup> Prescription stimulants are reported to be easily accessible on college campuses, and, as neural networks underlying decision-making and risk assessment are not fully mature until the mid-twenties, so is the tendency to experiment with stimulants or other substances for perceived benefit.<sup>56–58</sup> Young adulthood is the period wherein addiction and neuropsychiatric conditions are most likely to become symptomatic, making experimentation with powerful prescription medications and psychotropic substances rife with potential danger.<sup>56</sup> Alarming, the results of the 2018 National Survey on Drug Use and Health (NSDUH) showed that stimulant misuse eclipsed opioid misuse for the second year in a row, with 6.5% and 5.5% of young adults between 18 and 25 years of age misusing stimulants and opioids, respectively.<sup>59</sup>

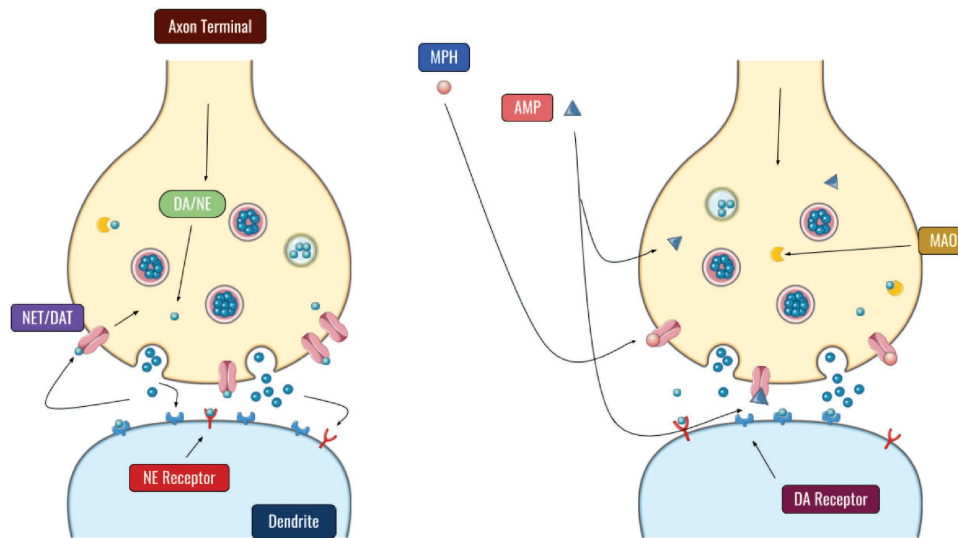
Most non-medical users of stimulants report obtaining the medication from their family, friends, or peers.<sup>18,19,60</sup> Interestingly, though effective long-term pharmacological management of ADHD is associated with overall decreased odds of developing a substance use disorder,<sup>61–63</sup> between 4% and 35% of college students diagnosed with ADHD report previous NMU of their medication.<sup>18</sup> Using data published between 2005 and 2019, I calculated the pooled prevalence of NMU among Americans aged 18 to 25 years, regardless of their educational status (Table 3). Although estimates ranged from 2% to 31%,<sup>60,85</sup> the estimated mean pooled prevalence of NMU among American young adults, including college students, is 9.21% (Table 3). The 2018 NSDUH found that compared to adults aged 26 years and older, young adults reported NMU between 3 times and 4 times more frequently.<sup>59</sup> Furthermore, Compton, the deputy director of the NIDA, and colleagues recently found young adults to have roughly 5 times the odds of initiating NMU than older adults.<sup>19,59</sup> Whether there is a statistically significant trend toward higher prevalence of NMU among the young adult population is difficult to ascertain given the wide range of estimates in the literature and lack of uniform measurement method. Although the NSDUH found a relatively stable 4-year prevalence of NMU among young adults, peer-reviewed publications almost uniformly vary from the official reports.<sup>59</sup> It is unclear why a complete picture of NMU among young adults has remained so elusive. Perhaps this is due to geographical differences or cultural idiosyncrasies among individual college campuses. Furthermore, this variance is multifactorial: definitions (or lack thereof) of NMU, sample size, classification of drugs, and methodology tend to differ from one study to the next.

**Table 3.** NMU Prevalence in Young Adults (including college students) Reported Between 2005 and 2019

Source	N	Prevalence
Teter et al, 2005	9161	5.4%
Teter et al, 2006	4580	5.9%
Lord et al, 2009	950	5.0%
Weyandt et al, 2009	363	8.9%
Upadhyaya et al, 2010	3307	2.1%
Rabiner et al, 2010	3407	8.9%
Clegg-Kraynok et al, 2011	492	7.0%
Garnier-Dykstra et al 2012	1253	17.7%
Lookatch et al, 2012	206	26.1%
Bavarian et al, 2013	520	25.6%
Hartung et al, 2013	1153	25.9%
Webb et al, 2013	144	15.0%
Wasserman et al, 2014	380	15.2%
Messina et al, 2014	1016	25.4%
Meisel & Goodie, 2015	279	17.2%
Cassidy et al, 2015	2073	11.3%
Gallucci et al, 2015	1020	12%
Weyandt et al, 2016	807	5.9%
Bavarian et al, 2017	554	16.6%
Kinman et al, 2017	988	23%
McCabe et al, 2018	4004	7.3%
Le et al, 2018	939	11.4%
Schulenberg et al, 2019	900	8.3%
<b>Pooled Prevalence</b>	<b>38,496</b>	<b>9.21%</b>

## Mechanisms of Action

The therapeutic effect of stimulants provides for greater attention to tasks at hand, access to working memory, planning, reward processing, and other relevant tasks that constitute executive functioning.<sup>7</sup> The two neurotransmitters associated with executive functioning, DA and NE, are highly concentrated in the prefrontal cortex (PFC) and act intimately in tandem. AMP and MPH are known to enhance DA and NE neurotransmission in the PFC by increasing



**Figure 2.** The schematic on the left depicts baseline DA and NE transmission. Much of the DA/NE undergoes reuptake into the presynaptic terminal, where it undergoes breakdown by monoamine oxidase (MAO), repackaging, or sequestration. The DA/NE that does make it into the synapse binds its respective receptor. AMP and MPH are shown on the right. AMP can diffuse through the cell membrane, where it can bind MAO and transporters. It can also bind to DAT's, MPH, on the other hand, is a strong inhibitor of NET's.

synaptic availability of DA and NE.<sup>43,45,86</sup> Interestingly, the mechanisms of action of AMP and MPH differ: MPH is a strong inhibitor of presynaptic dopamine transporters (DAT) and weak inhibitor of norepinephrine transporters, whereas AMP competitively inhibits DAT and norepinephrine transporters, increases DA release by inhibiting vesicular monoamine transporter 2, and blocks monoamine oxidase breakdown of DA and NE.<sup>43</sup> The product of both drugs, though, is the aforementioned amplified concentration of stimulatory neurotransmitters in the synaptic cleft and availability for use.<sup>14</sup> See Figure 2 for a simplified visual depiction of AMP and MPH mechanisms of action.

The therapeutic effect of AMP and MPH is dependent upon the rate of release, the dose, and the duration of activity of the formulation.<sup>14,87</sup> This therapeutic effect has an inverted U-shape: up to a point, the increased DA and NE that results from stimulant medications normalizes PFC neuronal activity and dysfunctional executive functioning seen in ADHD, but excessive DA and NE results in neuronal death, impaired inhibitory signaling, and downstream behavioral consequences.<sup>88-90</sup> Therapeutic formulations of MPH and AMP include extended-release and immediate-release and are designed to act along this U-shaped dose-response curve. Interestingly, the *d*-isomer of both AMP and MPH has more potent binding potential than the *l*-isomer for their respective receptors of interest.<sup>87</sup> Because *d*-AMP, the isoform most active in common pharmaceutical AMP, blocks reuptake of DA and increases DA and NE neuronal firing at therapeutic doses,<sup>43,87,91,92</sup> clinicians should be aware of AMP's broad activity across the brain.<sup>14</sup> This is especially true in those engaging in NMU, who commonly use supratherapeutic doses.<sup>85,93,94</sup> Although meta-analyses have shown MPH and AMP to produce comparable benefits in executive functioning, the two have subtly different mechanisms of action.<sup>95,96</sup> Like AMP, the *d*-isoform of MPH is the most active form, specifically binding PFC and striatal DAT in a dose-dependent relationship.<sup>97</sup> This pharmacokinetic similarity explains the shared increases in extracellular DA and NE seen, although MPH also agonizes 5-HT<sub>1A</sub>.<sup>43</sup> Adrenergic



receptors are activated, thus encouraging cortical excitability; guanfacine and clonidine, two non-stimulant medications used in ADHD management, have been shown to elicit similar effects.<sup>98</sup> MPH, in a fashion analogous to cocaine but not AMP, does not act directly as a DA/NE reuptake inhibitor; rather, MPH acts as an inverse agonist of DAT and NE transporters.<sup>99</sup> Lastly, as mentioned previously, MPH inhibits DAT to a greater extent than AMP and thus *indirectly* increases dopaminergic and noradrenergic transmission.<sup>43,97</sup>

## Molecular and Clinical Manifestations of AMP/MPH Neurotoxicity

### *Molecular—AMP*

Most individuals engaging in NMU of AMP experience rapid sensitization. This is due to upregulation of DAT to accommodate unnatural synaptic DA concentrations, and therefore greater doses of AMP are required to achieve the sought-after euphoric effect with each subsequent dose.<sup>100</sup> It is believed that behavioral reinforcement of euphoria, as well as sensitization (necessitating higher doses for effect),<sup>101</sup> is regulated by the nucleus accumbens (NAcc), the region of the brain most associated with reward processing, pleasure sensation, and other behavioral processes associated with addiction.<sup>43</sup> As dose increases beyond the therapeutic range, neurotoxic effects of greater DA concentrations begin to unfold in dopaminergic regions such as the NAcc, PFC, and the structures along the mesolimbic pathway.<sup>102</sup> With chronic high-dose (ie, suprathreshold) stimulant use comes alterations in dopamine receptors 2 and 3, presynaptic DA release and synthesis, and postsynaptic DAT availability, indicating a general attenuation of dopaminergic circuits.<sup>43,88,100,103</sup> In animal models, this is hypothesized to be the result of neuronal death due to oxidative stress.<sup>104,105</sup> In order to reach the euphoric effect many individuals seek by NMU, continued dose increases are necessary to break through tolerance, and, as the DA circuitry is already damaged, NMU escalation adds fuel to the fire. The rare psychoses reported among those who use stimulants appropriately, as well as the relatively common ones reported in non-medical users, are thought to arise from uncontrolled excitatory signaling resulting from aforementioned impairments in inhibitory signaling.<sup>88</sup> It is hypothesized that to compensate for toxic DA concentrations, affected neurons decrease their DA receptor and transporter availability to prevent subsequent excitatory overstimulation.<sup>100</sup> The downstream effect of this protective mechanism—diminished overall DA availability—results in neuropsychological dysfunction.

### *Molecular—MPH*

Unlike AMP, MPH's effects on DA and NE are due also to disinhibition of dopamine receptor 2 and activation of dopamine receptor 1.<sup>43</sup> In a murine model, chronic high-dose MPH exposure (10 mg/kg daily for 12 weeks) has been associated with increased oxidative stress in nigrostriatal dopaminergic neurons, specifically due to heightened sensitivity to the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).<sup>106</sup> MPTP is a strong substrate for the DA receptor and is tightly linked to the etiology and pathophysiology of Parkinson disease (PD).<sup>107</sup> Oakes and colleagues at East Tennessee State University recently described a dose-dependent elevation in striatal dopaminergic neuronal DA-quinone production with chronic MPH exposure in a murine model.<sup>108</sup> As the neuroimmune cascade is activated by oxidative stress, glutathione conjugates with the DA-quinone and sequesters it. Unfortunately, as glutathione reserves are depleted by chronic use, greater oxidative stress occurs. Although the majority of the literature regarding stimulant-induced neurotoxicity has focused on AMP, it is likely that the differential mechanisms of MPH-induced boosts in catecholamine concentration require specific

investigation. This is salient given the differential effects of MPTP on dopaminergic neurons exposed to MPH compared to AMP. Whether MPH differs from AMP in its proclivity to actually induce Parkinsonism in individuals with ADHD or non-medical users has yet to be assessed. Clinicians should consider available evidence from animal and epidemiological studies of MPH-induced neuropathology when choosing appropriate treatment for ADHD, especially if the patient has a family history of PD.

### *Clinical—AMP*

The most common clinical manifestations of AMP NMU-induced neurotoxicity include stroke, Parkinsonism, seizure, and psychosis.<sup>109</sup> As the mechanism of action of methamphetamine is very similar to that of AMP,<sup>110</sup> many of the potential adverse effects of methamphetamine use are liable in AMP NMU. The risk for hemorrhagic stroke, but not ischemic stroke, is increased between 5- and 7-fold among stimulant users under 45 years of age compared to those who do not use.<sup>109</sup> Acute cerebrovascular effects (eg, hypertension, tachycardia, cerebral vasospasm) and chronic use-induced effects (eg, apoptosis of vascular smooth muscle, atherosclerosis, inflammatory vascular processes) of stimulants have been reported to put users at increased later risk for arrhythmias and resultant thromboembolism.<sup>109</sup> PD is thought to result from reduced striatal DA, DAT, and morphological defects in dopaminergic neurons.<sup>111</sup> Given AMP NMU is observed to result in what are morphological precursors to PD, the increased risk (1.5–3 times) and earlier onset (median of 6 years) of PD among those who use high-dose stimulants is understandable.<sup>109,112</sup> The acutely augmented concentrations of DA associated with AMP NMU are also associated with lower concentrations of gamma-aminobutyric acid—the neurotransmitter involved in regulating excitatory and inhibitory signaling in the brain—and may lower seizure threshold.<sup>113</sup>

Finally, the occurrence of psychosis in those using AMP (2.4%) and the high prevalence of AMP-induced episodic psychoses' conversion to schizophrenia (~33%) are clinically salient.<sup>114,115</sup> Acute psychosis, though dynamic and complex, has long been associated with overactive DA signaling and transport.<sup>116</sup> The pathophysiology of ADHD, as mentioned above, also involves dysregulation of DA. Granted, the correlation between DA and ADHD symptomatology is inverted in psychosis, but individual risk factors are not infrequently shared between psychiatric disorders. Supratherapeutic doses common to NMU are able to manifest psychotic symptoms, but the normalizing influence therapeutic AMP has on ADHD-associated DA signaling makes psychosis exceedingly rare in patients with ADHD.<sup>117</sup> In the context of specifically AMP-induced psychosis, repeated use of high-dose stimulants in both therapeutic and misuse contexts is associated with greater blood-brain barrier porosity and tight-junction dysfunction.<sup>118</sup> Interestingly, AMP is associated with a 4-fold greater DA release compared to MPH, which likely contributes to the greater probability of AMP- than MPH-induced psychosis.<sup>119</sup> The treatment of both AMP-induced and organic psychoses involves dopamine receptor 2 blockade with antipsychotics with the intention to decrease overactive dopamine and associated transmission.<sup>115,116</sup> Interestingly, many patients who benefit from DA blockade report adverse effects similar to ADHD symptoms: diminished subjective well-being, self-control, and cognitive functioning, as well as lethargy and emotional dysregulation.<sup>120,121</sup>

### *Clinical—MPH*

MPH and AMP neurotoxicity is quite similar at the molecular level. This similarity can be mapped onto clinical outcomes, as well, with the important exception of psychosis. Moran

and colleagues recently reported results from a large cohort study of individuals using MPH and AMP for ADHD.<sup>119</sup> They found a 10-year incidence of 1.78 new psychotic episodes per 1000 person-years in those taking MPH compared to 2.83 new episodes per 1000 person-years in those taking AMP. The risk for stimulant-induced psychosis during the study period was also significantly attenuated in MPH-treated compared to AMP-treated patients (0.10% and 0.21%, respectively).<sup>119</sup> Interestingly, there also appears to be a greater risk for psychosis in patients treated with AMP by physicians without psychiatric training when compared to those treated by board-certified psychiatrists.<sup>119</sup> This highlights potential implications for the management of ADHD by primary care physicians and questions whether primary care should be the setting wherein ADHD is diagnosed, treated, and followed.

## Discussion

The NMU of stimulants by healthy adults leads to mixed results at best and significant decreases in neuropsychological performance at worst.<sup>46,122–124</sup> Much to the chagrin of healthy college students looking for a leg up, college grade point average and NMU are inversely correlated.<sup>71,123</sup> Attention, inhibitory control, short-term episodic memory, and delayed episodic memory may be slightly positively affected by NMU, but cognitive functions such as working memory are worsened.<sup>122</sup> Concerningly, students reporting their NMU in research settings fail to perceive that their use of stimulants carries risk of adverse effects or that NMU fails to produce positive changes that are worth the risk. It is therefore unlikely that deleterious neuropsychological and neurotoxic outcomes are being considered by those who engage in NMU. In contrast to NMU, the employment of prescription stimulants for ADHD is thought to be safe and effective for at least the short term.<sup>11</sup> Upregulation of DAT, normalization of structural abnormalities, and increased striatal DA availability are associated with long-term treatment with MPH in individuals with ADHD.<sup>7,125</sup> Working memory, response inhibition, and reaction time—domains commonly affected by ADHD—are reported to be positively impacted behavioral responses to the molecular and structural changes associated with treatment.<sup>7,126</sup>

The prevalence of prescription stimulant misuse in the adult population is deeply concerning at both the public health and clinical levels. This is compounded by the fact that the epidemiologic studies included in this review do not report a uniform estimated NMU prevalence. This may indicate a weak grasp by the public health community on the problem of stimulant NMU. Consideration of the stage of neurodevelopment that many adults reporting NMU are in, as well as the general dearth of literature considering long-term therapeutic use and NMU of prescription stimulants, will likely be of paramount importance to future clinicians treating ADHD and the potential negative sequelae of stimulant use. Future public health and clinical education should be augmented to include stimulant misuse trends and outcomes as practitioners in both arenas will likely encounter its effects as the population ages.<sup>127</sup> As clinician societies and government agencies begin requiring drug manufacturers to consider long-term effectiveness in their stimulant medications, it is likely ADHD pharmacotherapy will evolve.

With the exception of just two large-scale studies—the Multimodal Treatment Study of Children With ADHD and the Comparison of Methylphenidate and Psychotherapy in Adult ADHD Study (COMPAS)—the consideration of pharmacotherapy's potential benefits and risks for patients long term remains wholly inadequate.<sup>128–130</sup> For better or worse, current guidelines leave the formulation and dose of medication prescribed open to interpretation by clinicians.<sup>14</sup> The precarious state of ADHD treatment was recently debated in the *Journal of the American Academy of Child and Adolescent Psychiatry*.<sup>131,132</sup> Swanson,<sup>132</sup> a University of California,

Irvine professor of pediatrics and a principal investigator on the COMPAS, recently reported that the impressive effect sizes, symptom reduction, and behavioral outcomes associated with short-term pharmacotherapy have not conclusively been demonstrated to be maintained in the long term. In response to Swanson, Coghill,<sup>131</sup> a renowned child/adolescent psychiatrist and scientist at the University of Melbourne, wrote that current trials continue to find that long-term pharmacotherapy is indeed effective when used dynamically, pragmatically, and subject to new clinical insights. Coghill's argument was reinforced by two studies recently published in the *American Journal of Psychiatry*: one finding sustained MPH effectiveness over 2 years in pediatric ADHD and the other finding inverse associations between long-term treatment and risk for suicide and substance abuse, among other outcomes.<sup>133,134</sup>

Parallel to substantive change to the ADHD management landscape, long-term, robust exploration of differences in outcomes between individuals who begin treatment in adulthood versus childhood, potential unknown neurological outcomes in the contexts of both NMU and ADHD, and prescription stimulant toxicology is urgently needed. Questions related to long-term, consistent treatment with medication across the life span remain wide open to evidence-based and individualized study and conclusions, although the clinical recommendations in the *DSM-5* remain the gold standard given the current state of treatment options. Lastly, though this review of the literature is comprehensive, there are many basic unknowns concerning the relationship between prescription stimulants and neurotoxicity.

## Conclusion

This narrative review presented the current understanding of prescription stimulant-induced neurotoxicity in both licit and illicit categories found in the literature. Although the sparse data available suggest long-term treatment of ADHD to be associated with positive outcomes in educational, social, psychological, and emotional domains, it is unclear whether this is due to the medications' continued action or the development of coping mechanisms over time. Additionally, as much the same for individuals engaged in NMU of MPH and AMP, future work is needed to measure the risks to and outcomes in neurological functioning and safety in those being treated for ADHD. It is also important to note that, though a comprehensive range of publications was considered for use in this review, the sheer number of records available made universal consideration impossible. Finally, beyond the clinical monitoring and treatment of potential sequelae, the public health and clinical communities must play a significantly more engaged role in educating the public about the proper use of stimulants—especially if we aim to prevent increased presentation of prescription stimulant neurotoxicity in the future.

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## Searches

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