J Exp Clin Med 2013;5(6):210–216

Contents lists available at ScienceDirect

Journal of Experimental and Clinical Medicine

journal homepage: http://www.jecm-online.com

REVIEW ARTICLE

Stimulants, Wakefulness-promoting Agents, and Nonstimulant Attention Deficit Hyperactivity Disorder Medications

Shen-Chieh Chang [1], Winston W. Shen [1,2]*

[1] Department of Psychiatry, Wan Fang Medical Center, Taipei Medical University, Taipei, Taiwan
[2] Department of Psychiatry, College of Medicine, Taipei Medical University, Taipei, Taiwan

ARTICLE INFO

Article history:
Received: Oct 14, 2013
Revised: Oct 17, 2013
Accepted: Oct 22, 2013

KEY WORDS:
attention deficit hyperactivity disorder;
modafinil;
narcolepsy;
stimulants

The treatments for attention deficit hyperactivity disorder (ADHD) as well as for excessive daytime sleepiness of narcolepsy, obstructive sleep apnea/hyponea syndrome, and shift work sleep disorder have been advanced and expanded rapidly in the past 15 years. The pharmacotherapeutic armamentaria for those disorders include stimulants (amphetamine, methamphetamine, methylphenidate, and lisdexamfetamine), wakefulness-promoting agents (modafinil and armodafinil for narcolepsy), as well as nonstimulant ADHD medications (atomoxetin, a norepinephrine reuptake inhibitor; guanfacine and clonidine α_{2A} agonists). In this review, a brief history, chemical classifications, and pivotal clinical data of those therapeutic drugs which were approved as indications by the US Food and Drug Administration are discussed. Common off-label applications of those drugs in psychiatric practice are also mentioned.

1. Introduction

Stimulants, also known as psychostimulants, can increase patients' motivation, mood, energy, and wakefulness.[1] They include naturally occurring substances such as cocaine and caffeine as well as synthetic drugs such as amphetamine and methylphenidate. The use of naturally occurring substances use can be traced back to ancient Peru and other pre-Columbian Andean societies.[2] In 1883, German physician Aschenbrandt gave cocaine to members of the Bavarian army, and found that the drug suppressed their appetite and enhanced their mental powers and endurance in maneuvers.[3] Sigmund Freud used a great deal of cocaine himself and published a review called *Über Coca*, describing its physiological effects and potential therapeutic uses.[4]

Amphetamine, first synthesized in 1887, was also used extensively by both sides of the conflict during World War II to combat fatigue, increase alertness, and improve the mood of the soldiers. Its abuse began to rise after the war, and became common in the 1960s and 1970s.[2] This use is still popular, especially for fighter pilots on long-distance fights.[5] Now, stimulants are indicated for treating attention deficit hyperactivity disorder (ADHD) and the excessive daytime sleepiness of narcolepsy, although they are also effective briefly in treating depression and suppressing appetite. The Food and Drug Administration (FDA) of the USA coined and approved new stimulants such as modafinil and armodafinil (orexin/hypocretin activator), as wakefulness-promoting agents for the indication of treating excessive daytime sleepiness of narcolepsy. Since the first nonstimulant ADHD medication atomoxetine was brought to the market in 2002, another two nonstimulants have been approved to treat ADHD.

In this review, we intend to describe briefly the chemical classifications and their pharmacotherapies with stimulants, wakefulness-promoting agents, and nonstimulants in treating ADHD. Pivotal clinical drug trials of those medications will be highlighted, and the treatment implications of those medications discussed.

2. Chemical classification of stimulants and wakefulness-promoting agents

Sympathomimetic drugs can stimulate the sympathetic nervous system by directly serving as adrenergic receptor agonists or by indirectly increasing the release of the neurotransmitter norepinephrine at postganglionic nerve endings.[6] Most centrally active stimulants used in psychiatry are indirectly acting sympathomimetic drugs, with the primary effect of causing the release of catecholamines from presynaptic neurons.[1] They include amphetamine, dextroamphetamine, methamphetamine, lisdexamfetamine, methylphenidate, and dexmethylphenidate. The mechanism of the novel wakefulness-promoting agents (modafinil

* Corresponding author. Winston W. Shen, Department of Psychiatry, Wan Fang Medical Center, Taipei Medical University, 111, Section 3, Hsing Long Road, Taipei, Taiwan.
E-mail: W.W. Shen <shenwinw@gmail.com>

1878-3317/$ – see front matter
http://dx.doi.org/10.1016/j.jecm.2013.10.010

and armodafinil) is presumably acting on brain orexin/hypocretin neurons, although other mechanisms remain under debate.

2.1. Amphetamine family

2.1.1. Amphetamine

Amphetamine, abbreviated from alpha-methyl-phenyl-ethyl-amine (a-m-ph-et-amine), is structurally known as phenyl-isopropylamine.[7] Chemical substitutions on the phenyl group, isopropyl chain or amine group result in producing various chemicals with different mechanisms.

Amphetamine, which is highly lipid-soluble, rapidly distributes into tissues and transits across the blood–brain barrier, achieving peak levels in about 2 hours. Amphetamine competitively inhibits reuptake of dopamine (DA) into the presynaptic neuron by binding to the DA transporter (DAT). Amphetamine also acts as a substrate of DAT itself and triggers its own transport into the presynaptic neuron. It has a similar effect on the vesicular monoamine transporter, inhibiting reuptake of DA and entering into the synaptic vesicles. DA displacement from synaptic vesicles by amphetamine causes intracellular DA accumulate, causing channels to open and release DA into the synapse.[8]

Amphetamine acts similarly on the norepinephrine (NE) transporter (NET). It inhibits reuptake of NE from the synapse, and is transported into the presynaptic neuron terminal itself, resulting in increased NE levels in the synapse.[9] In DAT-knockout mice, DA is not released into the synaptic cleft after giving amphetamine[10]; however, NET-knockout mice are hyper-responsive to the locomotor stimulation of amphetamine, and have DA D_2/D_3 receptor supersensitivity.[11] Further studies are needed to clarify the possible differences in actions of stimulants on DAT and NET. Like tranylcypromine, a substituted amphetamine, which acts as a monoamine oxidase (MAO) inhibitor, amphetamine itself is also a weak and reversible MAO inhibitor.[12]

2.1.2. Dextroamphetamine

Amphetamine has two stereoisomers. Compared to the *levo*-isomer, dextroamphetamine, or *d*-amphetamine, is about four times more potent in increasing DA efflux, yet has no significant difference in the potencies on NE efflux.[13] Dextroamphetamine is about two times more potent than the *levo*-isomer in improving wakefulness, but has equal potency in reducing cataplexy and rapid eye movement sleep.[14]

2.1.3. Lisdexamfetamine

Lisdexamfetamine is a pharmacologically inactive prodrug, and is metabolized to dextroamphetamine and L-lysine in the red blood cells by rate-limited enzymatic hydrolysis.[13] Compared to dextroamphetamine, lisdexamfetamine produces a gradual and sustained increase in dopamine efflux. It has fewer pleasurable effects and helps to lower its addition risk.[13]

2.1.4. Methamphetamine

Methamphetamine has an additional methyl group attached to the amine of amphetamine. This addition makes this derivative more lipophilic, thus enabling rapid and extensive transport across the blood–brain barrier and giving a better central over peripheral profile.[15] The half-life of methamphetamine is about 9–12 hours, and its major metabolic pathways include aromatic hydroxylation producing 4-hydroxymethamphetamine and *N*-demethylation to form amphetamine.[16] However, the contribution of amphetamine metabolite does not cause much change in subjective effects added to methamphetamine, and the peak amphetamine levels are substantially lower than those of the parent drug throughout the studied time.[16] That methamphetamine is highly addictive and more neurotoxic than amphetamine is believed to be due to its rapid absorption into the central nervous system (CNS), its potency in a sustained release of brain DA and glutamate, resulting in neurotoxic insults on brain neurons.[7]

2.1.5. Methylphenidate

Methylphenidate has a piperidine ring structure attached to the chain of amphetamine. It is fairly short-acting, with the effects lasting about 4 hours and a half-life of 3 hours.[7] Methylphenidate inhibits NET and DAT, and acts as a more potent and effective NE and DA reuptake inhibitor than bupropion.[9] It does not cause the release of newly synthesized cytosolic DA as amphetamine does,[17] and does not work on vesicular monoamine transporter or act as a pseudosubstrate for DAT and NET.[9] Methylphenidate has a lower reinforcing efficacy, resulting in having a lower abuse liability than dextroamphetamine.[18] Dexmethylphenidate, a *d*-isomer of methylphenidate, is more potent than the *l*-isomer on both DAT and NET binding.[9]

2.2. Wakefulness-promoting agents

2.2.1. Modafinil

Modafinil and armodafinil have a different mechanism of action, which is distinctive from the amphetamine family. They are designated as wakefulness-promoting agents by the US FDA. How modafinil acts to promote wakefulness is still debatable. Although modafinil has a weak affinity for DAT, its abolished effect in DAT knockout mice still suggests that the dopaminergic system plays a role in modafinil.[19]

Hypocretin, also called orexin, is an excitatory neuropeptide synthesized by neurons in perifornicular area located in the lateral posterior hypothalamus. The orexin neurons project widely and heavily innervate all of the arousal regions, with particularly dense innervation of the locus coeruleus and tuberomammillary nucleus (TMN), and play essential roles in regulating wakefulness and sleep.[20] The TMN is the sole neuronal source of histamine in the brain, and is thus necessary for maintaining normal wakefulness.[21] Modafinil activates orexin neurons and the TMN.[21]

Luca and colleagues did a series of studies showing that racemic mixtures of modafinil increase glutamate and decrease GABA levels in posterior hypothalamus and medial preoptic area,[22,23] and that modafinil increases glutamate in the hippocampus and ventral thalamus.[24] These findings may contribute to its wakefulness-enhancing property. Other studies showed that modafinil's effects are mediated through activating NE α_1 receptors, because its wake-promoting effects in experimental animals are inhibited by central α_1 blockers such as prozosin.[25]

2.2.2. Armodafinil

Armodafinil {(−)-2-[(R)-(diphenylmethyl) sulfinyl] acetamide} is the active (−)-R-enantiomer of racemic modafinil. At the same dosage as modafinil, armodafinil can have a late concentration peak, and the higher plasma concentrations maintain its effect for 6–14 hours after receiving the drug.[26]

3. FDA-approved indications and off-label uses for stimulants and wakefulness-promoting agents

The data of double-blind, randomized, controlled trials examining their safety, efficacy, and effectiveness of stimulants are only limited in ADHD, although they have been used for decades in clinical practice. Here, we present FDA-approved indications with related pivotal drug trials first. We also discuss the clinical data of their off-label use.

3.1. ADHD

In theory, ADHD symptoms are linked to insufficient information processing by pyramidal neurons in the prefrontal cortex, which may be partly due to imbalances in the neurotransmitters DA and NE.[27] Stimulants act directly in the prefrontal cortex to enhance signal strength by increasing NE and to reduce noise by increasing DA, resulting in reducing symptoms of inattention, hyperactivity, and impulsivity in ADHD.[27] Studies have also shown that stimulants bind to the DAT in the striatum and indirectly enhance prefrontal cortical function through striatal-prefrontal pathways.[28]

Bradley[26] first reported in 1937 that *d*- and *l*-amphetamine improve school performance, social interactions, and emotional responses in children with behavioral disorders. His studies have an important influence on the studies of methylphenidate and ADHD, although this study had been ignored in the field of child psychiatry for decades.[29]

In 1955, methylphenidate was approved by the US FDA (www.fda.gov). By 1996, 155 controlled studies of 5768 children, adolescents, and adults had documented the efficacy of stimulants in an estimated 70% of patients.[30] Of the stimulants studied, methylphenidate comprised 83% of all the studies.[30] Short-term randomized clinical trials of stimulants—most often ≤12 weeks in duration—have been reported robust efficacy of methylphenidate, *d*-amphetamine, and pemoline in children with ADHD, with equal efficacy between stimulants.[31]

Pragmatic issues associated with amphetamines and methylphenidate, such as the need for frequent doses and resulting problems in compliance, have led to developing long-acting formulations.[28] Methylphenidate in an osmotic controlled release oral delivery system (OROS) is designed to have a 12-hour duration of effect, and the mean time to reach peak plasma concentrations occurs at 6–10 hours (www.fda.gov). Methylphenidate transdermal system is designed to continuously release the drug by applying the patch to the skin.[32] Its advantages are for hyperactive children who have difficulties swallowing pills. The transdermal system patch continues to deliver the medication until it is removed but about half of the children have shown at least minor erythematous reactions.

In the Multimodal Treatment Study of ADHD, which was funded by the National Institute of Mental Health of the USA, 579 children with ADHD combined type, aged 7–9.9 years, were assigned to 14 months of medication management with methylphenidate; intensive behavioral treatment; the two combined; or standard community care.[33] The results showed that medication management and combined treatment are better than behavioral treatment and community care in reducing children's ADHD symptoms.[33] This study shows the superiority of stimulants over the nondrug treatment in treating the core ADHD symptoms in child patients. Medications approved by the FDA for treating ADHD include dextroampetamine, amphetamine, dextroamphetamine, lisdexamfetamine, methylphenidate, and dexmethylphenidate.[34] Detailed information is available at www.pediatrics.aappublications.org/content/suppl/2011.10/11/peds.2011. Although methamphetamine carries an FDA-approved indication for ADHD and external obesity, it is not favored by many experts because of its highly addictive nature and suspected neurotoxicity in animal data.[35]

The results of the analysis of pooled data from three randomized, double-blind, placebo-controlled studies showed that modafinil can improve symptoms of ADHD (assessed by ADHD rating scale IV School Version).[36] Similar improvements have also been observed on the ADHD rating scale IV Home Version.[37] But due to the reports of serious skin rash, including Stevens–Johnson syndrome, and hypertension, modafinil has not been approved by the US FDA in pediatric patients for any indications, including ADHD and narcolepsy (www.fda.gov).

3.2. Excessive daytime sleepiness and sleep attacks in narcoleptic patients

Narcolepsy is a rapid eye movement sleep disorder, characterized by the classic four symptoms of excessive daytime sleepiness with irresistible sleep attacks, cataplexy, hypnagogic hallucination, and sleep paralysis.[37] Narcolepsy has been identified to be associated with *HLA-DR2* and *DQB1*0602*,[38] encoding proteins to regulate the production for abnormal hypocretin transmission.[39] Hypocretin deficiency may decrease monoaminergic tone, and could explain the beneficial effect of medications that can increase monoamine. These findings may also suggest that the daytime sleepiness in narcoleptic patients is treated via an increase in hypocretin transmission.[39]

Stimulants such as amphetamine or methylphenidate have been used for excessive daytime sleepiness and sleep attacks since the 1930s,[37] but have limited information available on the benefit-to-risk ratio.[37] The lack of information may reflect the limited research funding sources for generic medications rather than clinical use of these drugs.[40] In a nonrandomized controlled study, methylphenidate and *d*-amphetamine significantly improved both objective and subjective values for somnolence as well as cognitive function as measured by a digit symbol substitution test.[41] Amphetamine, methamphetamine, *d*-amphetamine, and methylphenidate remain the drug of choice for sleepiness due to narcolepsy, recommended by the American Academy of Sleep Medicine.[40]

As stated previously, the efficacy of modafinil which is different from that of stimulants, is through activating orexin neurons in the perifornical area.[21] In a nonrandomized control study, healthy volunteers received modafinil, *d*-amphetamine and placebo orally 30 minutes prior to bedtime. Modafinil does not impair total sleep time and sleep efficiency, and does not alter sleep architecture such as reduction of sleep Stage 2 and rapid eye movement-sleep.[42] The result of a meta-analysis of nine randomized controlled trials showed that modafinil improves excessive daytime sleepiness in patients with narcolepsy assessed by the subjective Epworth Sleepiness Scale, objective multiple sleep latency test, and maintenance of wakefulness test.[43] However, modafinil cannot decrease daily number of attacks of cataplexy.[43]

In 1998, the US FDA approved modafinil for treating excessive daytime sleepiness in patients with narcolepsy. In 2004, new indications were approved to improve wakefulness in two excessive sleepiness patient populations with obstructive sleep apnea/hypopnea syndrome and with shift work sleep disorder. Armodafinil was later approved to treat excessive daytime sleepiness with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder in 2007 (www.fda.gov).

Besides the stimulants and wakefulness-promoting agents, sodium oxybate, the sodium salt of γ-hydroxybutyric acid (GHB), was approved by the FDA for reducing both cataplexy and excessive daytime sleepiness in patients with narcolepsy.[44] GHB is a natural metabolite of GABA. Its exact mechanism of action is not known, yet studies suggest that at pharmacological doses, GHB activates $GABA_B$ receptor and alters sleep architecture,[45] possibly through the release of both DA and serotonin.[44]

4. Off-label uses and promising indications

4.1. Depression

Case series have suggested the efficacy of stimulants combined with monoamine oxidase inhibitors and tricyclic antidepressant in

patients with treatment-resistant depression.[45,46] In outpatients with major depressive disorder who had failed from one to three previous antidepressant monotherapies, methylphenidate OROS augmentation cannot improve patients' depressive symptom scores (rated by the Montgomery–Åsberg Depression Rating Scale) at endpoint after 5 weeks, although both apathy (measured by the Apathy Evaluation Scale) and fatigue (measured by the Multidimensional Assessment of Fatigue) are improved.[47]

The results of a pooled analysis of two randomized, double-blind, placebo-controlled studies of modafinil augmentation for patients who were partial responders to adequate selective serotonin reuptake inhibitor therapy with excessive sleepiness and fatigue showed that modafinil augmentation rapidly (within 1 week) improves overall clinical condition (measured by the Clinical Global Impression–Improvement), wakefulness (Epworth Sleepiness Scale), depressive symptoms (17-item Hamilton depression scale), and fatigue (Fatigue Severity Scale). At final visit, patients with modafinil augmentation still shows their improvement in overall clinical condition, wakefulness, and depressive symptoms.[48]

4.2. Obesity

Since 1937, a series of reports and studies have shown that amphetamine can be used to treat obesity in adults and children; it was thought that inhibiting food intake is achieved through the release of NE in the CNS.[49] A small, short-term study has suggested that modafinil also has anorectic effect.[50] But the duration of appetite-suppressing effects of the stimulants can last only for the first few weeks, and their high abuse potential also limits their clinical use.[1]

Methamphetamine was approved by the US FDA to treat exogenous obesity as a short-term (i.e., a few weeks) adjunct in a regimen of weight reduction based on caloric restriction, for adult patients whose obesity is refractory to alternative therapy (www.fda.gov). There are other amphetamine derivatives that are approved for obesity treatment in adults, such as benzphetamine, phendimetrazine, diethylpropion, and phentermine.[49]

4.3. Schizophrenia

Although a long-term use of stimulants such as amphetamines, can worsen psychosis in schizophrenic patients, they may still improve negative symptoms without worsening of positive symptoms in selected patients who are stable and treated with effective antipsychotic medications.[51] There are no consistent data about the benefit of adding modafinil or armodafinil to an antipsychotic regime in enhancing cognitive function, attenuating fatigue, enhancing activity, improving negative symptoms, and reducing weight in patients with schizophrenia.[52]

4.4. Fatigue

The use of stimulants to improve fatigue in military operations and/or specific medical conditions may be due to the belief of their pharmacological effects, but related evidence from large-scale controlled studies is not available.[7] *d*-Amphetamine and methylphenidate can improve fatigue in patients with human immunodeficiency virus (HIV).[53,54] Methylphenidate is also effective in treating fatigue in patients with Parkinson's disease and cancers.[55,56]

Modafinil has been extensively studied to treat fatigue in specific medical conditions for patients with multiple sclerosis, Parkinson's disease, chronic fatigue syndrome, HIV, dementia, and fibromyalgia, and most results are promising.[57]

4.5. Cocaine and amphetamine/methamphetamine use

As a replacement treatment strategy, double-blind studies have shown that sustained release *d*-amphetamine and methamphetamine can reduce cocaine use, but methylphenidate has not shown the same effect.[58,59] Preliminary trials showed that modafinil decreased cocaine-induced euphoria, but most recent data fail to support that it can decrease cocaine use.[58]

There were scarce data to show that sustained release d-amphetamine/ methamphetamine, as well as methylphenidate and modafinil cut down amphetamine/ methamphetamine use, and future studies are needed.[58]

4.6. Strokes and traumatic brain injury

The limited clinical studies have shown that stimulants (such as amphetamine and methylphenidate) and modafinil have rehabilitative effects in patients with strokes or traumatic brain injury, due to improving their arousal and cognition as well as facilitating functional recovery.[59]

5. Nonstimulant medications for ADHD

5.1. Atomoxetine

The US FDA has approved three nonstimulants for the treatment for ADHD (www.fda.gov). Atomoxetine is the first nonstimulant drug for this indication.[32] A meta-analysis of nine randomized placebo-controlled trials showed that atomoxetine can reduce core ADHD symptoms. The treatment response and relapse prevention for ADHD through the use of atomoxetine are good.[60]

Being a selective NE reuptake inhibitor, atomoxetine has little or no affinity for other neurotransmitter receptors.[61] However, atomoxetine can also increase prefrontal DA levels due to inhibiting NET-mediated DA uptake, as the NET is relatively abundant compared with the DAT level in the prefrontal cortex, and DA can be taken up nonselectively by the NET.[62] Studies also showed that the increased NA in the prefrontal cortex may activate DA neurons, resulting in an increase in the extracellular DA levels.[62] Patients need to be maintained at the full therapeutic dose for at least several weeks to obtain the drug's full effect.[63]

Compared to traditional stimulants, atomoxetine's efficacy does not differ significantly from that of immediate-release methylphenidate, but significantly less than those of methylphenidate OROS and extended-release mixed amphetamine salts.[61] A 2007 consensus has recommended stimulants as the first line of treatment for ADHD, particularly when no comorbidity is present, whereas atomoxetine may be considered as the first drug for ADHD in individuals with an active substance abuse problem, comorbid anxiety, or tics.[63]

A meta-analysis of 14 trials on suicide-related behavior in pediatric patients treated with atomoxetine and placebo showed that the frequency of suicidal ideation was 0.37% (5/1357) for the placebo group, but no patient who received atomoxetine committed suicide (0/851).[64] However, the US FDA has placed a black box warning on atomoxetine about increased suicide ideations in children and adolescents as a class action because atomoxetine is an antidepressant pharmacologically in the class of a selective NE reuptake inhibitor (www.fda.gov).

5.2. Alpha$_2$ agonists (guanfacine and clonidine)

Large, randomized, double-blind, placebo-controlled trials have shown that guanfacine extended-release (XR) and clonidine XR can reduce ADHD rating scale IV total scores.[65,66] The US FDA approved

Table 1 Stimulants, wakefulness-promoting agents, and nonstimulants attention deficit hyperactivity disorder (ADHD) medications

Medication	Mechanism	Abuse potential	DEA schedule in the US	Indication for ADHD	Indication for excessive daytime sleepiness in		
					Narcolepsy	OSA	SWSD
d-Amphetamine	Sympathomimetic	++	II	Y	Y	N	N
Lisdexamfetamine	Sympathomimetic	++	II	Y	N	N	N
Methylphenidate	Sympathomimetic	++	II	Y	Y	N	N
Modafinil	Hypocretin/orexin activator and others	+	IV	N	Y	Y	Y
Armodafinil	Hypocretin/orexin activator and others	+	IV	N	Y	Y	Y
Atomoxetine	Norepinephrine reuptake inhibitor	0	0	Y	N	N	N
Guanfacine XR	α_{2A} agonist	0	0	Y^1	N	N	N
Clonidine XR	α_{2A} agonist	0	0	Y^1	N	N	N

DEA = Drug Enforcement Administration; N = no; OSA = obstructive sleep apnea; SWSD = shift work sleep disorder; Y = yes (monotherapy); Y^1 = yes (also as an adjuvant to stimulant); XR = extended release.
Note. From "Stimulants and wakefulness-promoting agents" by W.W. Shen 2011,[69] in *Clinical psychopharmacology for the 21st century*, 3rd ed (Shen W.W., ed), Copyright Ho Chi Publishing Company. Reprinted with permission.

them as a monotherapy or an adjunct to traditional stimulants to treat ADHD in 2007 (www.fda.gov).

Guanfacine and clonidine are both α_2 agonists. Guanfacine binds more selectively to α_{2A} receptors, producing fewer side effects of sedation and lowing less blood pressure, whereas clonidine binds to all three subtypes of α_2 receptors (including α_{2A}, α_{2B}, and α_{2C} receptors).[67] Most studies have focused on the negative feedback through presynaptic α_2 receptors, and many α_2 receptors in the CNS are actually localized postsynaptic to NE cells such as locus coeruleus. However, only those α_2 receptors, specifically α_{2A} subtype, mainly regulate the prefrontal cortex function.[68] Evidence has confirmed that the α_{2A} agonists can enhance both dorsolateral prefrontal cortex function (in regulating attention and action) and ventromedial prefrontal cortex function (in regulating emotion).[68]

6. Discussion

Table 1 summarizes clinical characteristics of all medications described in this review.[69] Few medications have received as much public scrutiny as those stimulants used to treat ADHD, despite their safety and efficacy being well-established. Their high abuse potential and presumed cardiovascular side effect, which is thought to be related to their effects to increase heart rate and blood pressure, largely restrict their clinical practice, although the two latest large studies indicate that ADHD medications (including stimulants and atomoxetine) do not increase the risk of serious cardiovascular events in children and adults.[70,71]

ADHD is one of the most common childhood onset psychiatric disorders, affecting 5–12 % of children. As many as 60% of child patients continue to meet ADHD criteria or have some symptoms as adults.[35] Although a worldwide survey estimated the average prevalence of adult ADHD to be about 3.4% in individuals aged 18–44 years, it remains largely underrecognized.[72] Short-term studies show that effect sizes of stimulants and those of nonstimulants in treating ADHD in adults are similar as in school-age children when robust doses are used.[73] The data of the effectiveness and safety of methylphenidate transdermal system, and adjunctive therapy with clonidine XR and guanfacine in adult ADHD are still lacking.

Many stimulants and wakefulness-promoting agents are used nonmedically as "smart pills," "study drugs," or for daytime sleepiness due to jet lag. Research found that up to 16% of students in some US colleges admitted using stimulants to maximize their learning power.[74] It has become such a hot issue that a commentary article in the journal *Nature* advocated that mentally competent adults can engage in cognitive enhancement using this kind of drugs.[75]

Since modafinil was first introduced to the market in 1998, research and development in this field began to flourish actively. New drugs such as atomoxetine as well as old drugs (guanfacine and clonidine) came to the market for the indication for ADHD. Other ADHD medications with novel mechanisms, such as nicotinic acetylcholine receptor agonist, are in the pipeline of drug development.[76] Interestingly, a small pilot study in 2008 also showed the promising effect of aripiprazole to reduce ADHD symptoms and improve overall functioning.[77]

Psychiatrists do not have many choices in Taiwan. Methylphenidate is the only stimulant in the market in both immediate release and OROS formulations. Atomoxetine is the only nonstimulant ADHD medication, although clonidine is available, but not in extended release formulation. Modafinil is indicated for narcolepsy. We hope that more novel medications will be introduced to Taiwan to benefit those patients with ADHD and narcolepsy, who do not respond well to the presently available medications or cannot tolerate their side effects.

Conflicts of interest

The authors declare no conflicts of interest with all the drugs mentioned in this article. The readers are encouraged to read the dosage levels of the drugs in their package inserts prior to prescribing to their patients.

This is an updated and expanded version of Chapter 6: Psychostimulants and Wakefulness-promoting Agent, in Shen WW. Clinical Psychopharmacology for the 21st Century, 3rd Edition. Taipei: Ho-Chi Book Publishing Company (in Mandarin), 2011.[69]

References

1. Sadock BJ, Sadock VA. Sympathomimetics and related drugs. In: Sadock BJ, Sadock VA, editors. *Kaplan and Sadock's synopsis of psychiatry: behavioral sciences/clinical psychiatry*. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 1098–103.
2. Kaminski M, Sjøgren P. The use of psychostimulants in palliative and supportive treatment of cancer patients. *Adv Palliat Med* 2007;**6**:23–31.
3. Aschenbrandt T. Die physiologische wirkung und die bedeutung des cocains. *Deutsche Medizinische Wochenschrift* 1883;**9**:730–2 [in German].
4. Markel H. *Über coca*: Sigmund Freud, Carl Koller, and cocaine. *JAMA* 2011;**305**:1360–1.
5. Caldwell JA, Caldwell JL, Darlington KK. Utility of dextroamphetamine for attenuating the impact of sleep deprivation in pilots. *Aviat Space Environ Med* 2003;**74**:1125–34.
6. *Mosby's Medical Dictionary*. 8th ed. St. Louis, Missouri, USA: Mosby/Elsevier; 2009, ISBN: 978-0-323-05290-0.
7. Ballas CA, Evans DL, Dinges DF. Psychostimulants and wakefulness-promoting agents. In: Schatzberg AF, Nemeroff CB, editors. *The American psychiatric publishing textbook of psychopharmacology*. 4th ed. Arlington: Virginia: American Psychiatric Publishing; 2009. p. 843–60.
8. Sulzer D, Sonders MS, Poulsen NW, Galli A. Mechanisms of neurotransmitter release by amphetamines: a review. *Prog Neurobiol* 2005;**75**:406–33.

9. Stahl SM. Attention deficit hyperactivity disorder and its treatment. In: Stahl SM, editor. *Stahl's essential psychopharmacology: neuroscientific basis and practical applications*. 3rd ed. New York: Cambridge University Press; 2008. p. 863–97.
10. Jones SR, Gainetdinov RR, Wightman RM, Caron MG. Mechanisms of amphetamine action revealed in mice lacking the dopamine transporter. *J Neurosci* 1998;**18**:1976–86.
11. Xu F, Gainetdinov RR, Wetsel WC, Jones SR, Bohn LM, Miller GW, Wang YM. Mice lacking the norepinephrine transporter are supersensitive to psychostimulants. *Nat Neurosci* 2000;**3**:465–71.
12. Stahl SM. Antidepressants. In: Stahl SM, editor. *Stahl's essential psychopharmacology: neuroscientific basis and practical applications*. 3rd ed. New York: Cambridge University Press; 2008. p. 511–666.
13. Heal DJ, Smith SL, Gosden J, Nutt DJ. Amphetamine, past and present—a pharmacological and clinical perspective. *J Psychopharmacol* 2013;**27**:479–96.
14. Kanbayashi T, Honda K, Kodama T, Mignot E, Nishino S. Implication of dopaminergic mechanisms in the wake-promoting effects of amphetamine: a study of D- and L-derivatives in canine narcolepsy. *Neuroscience* 2000;**99**:651–9.
15. Barr AM, Panenka WJ, MacEwan GW, Thornton AE, Lang DJ, Honer WG, Lecomte T. The need for speed: an update on methamphetamine addiction. *J Psychiatry Neurosci* 2006;**31**:301–13.
16. Schep LJ, Slaughter RJ, Beasley DM. The clinical toxicology of metamfetamine. *Clinical Toxicol* 2010;**48**:675–94.
17. Chiueh CC, Moore KE. Blockade by reserpine of methylphenidate-induced release of brain dopamine. *J Pharmacol Exp Ther* 1975;**193**:559–63.
18. Leonard BE, McCartan D, White J, King DJ. Methylphenidate: a review of its neuropharmacological, neuropsychological and adverse clinical effects. *Hum Psychopharmacol Clin Exp* 2004;**19**:151–80.
19. Schwartz JR. Modafinil: new indications for wake promotion. *Expert Opin-Pharmacother* 2005;**6**:115–29.
20. España RA, Scammell TE. Sleep neurobiology from a clinical perspective. *Sleep* 2011;**34**:845–58.
21. Scammel TE, Estabrooke IV, McCarthy MT, Chemelli RM, Yanagisawa M, Miller MS, Saper CB. Hypothalamic arousal regions are activated during modafinil-induced wakefulness. *J. Neurosci* 2000;**20**:8620–8.
22. Ferraro L, Antonelli T, Tanganelli S, O'Connor WT, Perez de la Mora M, Mendez-Franco J, Rambert FA. The vigilance promoting drug modafinil increases extracellular glutamate levels in the medial preoptic area and the posterior hypothalamus of the conscious rat: prevention by local GABAA receptor blockade. *Neuropsychopharmacology* 1999;**20**:346–56.
23. Ferraro L, Tanganelli S, O'Connor WT, Antonelli T, Rambert F, Fuxe K. The vigilance promoting drug modafinil decreases GABA release in the medial preoptic area and in the posterior hypothalamus of the awake rat: possible involvement of the serotonergic 5-HT3 receptor. *Neurosci Lett* 1996;**220**:5–8.
24. Ferraro L, Antonelli T, O'Connor WT, Tanganelli S, Rambert F, Fuxe K. The antinarcoleptic drug modafinil increases glutamate release in thalamic areas and hippocampus. *Neuroreport* 1997;**8**:2883–7.
25. Duteil J, Rambert FA, Pessonnier J, Hermant JF, Gombert R, Assous E. Central alpha 1-adrenergic stimulation in relation to the behaviour stimulating effect of modafinil; studies with experimental animals. *Eur J Pharmacol* 1990;**180**:49–58.
26. Dinges DF, Arora S, Darwish M, Niebler GE. Pharmacodynamic effects on alertness of single doses of armodafinil in healthy subjects during a nocturnal period of acute sleep loss. *Curr Med Res Opin* 2006;**22**:159–67.
27. Stahl SM. Mechanism of action of stimulants in attention-deficit/hyperactivity disorder. *J Clin Psychiatry* 2010;**71**:12–3.
28. Ford RE, Greenhill LL, Ponsner K. Stimulants. In: Martin A, Schahill L, Charney DS, Leckman JF, editors. *Pediatric psychopharmacology: principles and practice*. New York: Oxford University Press; 2003. p. 255–63.
29. Strohl MP. Bradley's benzedrine studies on children with behavioral disorders. *Yale J Biol Med* 2011;**84**:27–33.
30. Spencer T, Biederman J, Wilens T, Harding M, O'Donnell D, Griffin S. Pharmacotherapy of attention-deficit hyperactivity disorder across the life cycle. *J Am Acad Child Adolesc Psychiatry* 1996;**35**:409–532.
31. Greenhill LL, Halperin JM, Abikoff H. Stimulant medications. *J Am Acad Child Adolesc Psychiatry* 1999;**38**:503–12.
32. Sadock BJ, Sadock VA. Attention-deficits disorders. In: Sadock BJ, Sadock VA, editors. *Kaplan and Sadock's synopsis of psychiatry: behavioral sciences/clinical psychiatry*. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 1206–17.
33. The MTA. Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 1999;**56**:1073–86.
34. Subcommittee on Attention-Deficit/Hyperactivity Disorder; Steering Committee on Quality Improvement and Management, Wolraich M, Brown L, Brown RT, DuPaul G, Earls M, et al. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics* 2011;**128**:1007–22.
35. Spetie L, Arnold E. Attention-deficit/hyperactivity disorder. In: Martin A, Volkmar FR, editors. *Lewis's child and adolescent psychiatry: a comprehensive textbook*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 430–54.
36. Wigal SB, Biederman J, Swanson JM, Yang R, Greenhill LL. Efficacy and safety of modafinil film-coated tablets in children and adolescents with or without prior stimulant treatment for attention-deficit/hyperactivity disorder: pooled analysis of 3 randomized, double-blind, placebo-controlled studies. *Prim Care Companion J Clin Psychiatry* 2006;**8**:352–60.
37. Akintomide GS, Rickards H. Narcolepsy: a review. *Neuropsychiatr Dis Treat* 2011;**7**:507–18.
38. Mignot E. Genetic and familial aspects of narcolepsy. *Neurology* 1998;**50**(Suppl. 1):S16–22.
39. Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E. Hypocretin (orexin) deficiency in human narcolepsy. *Lancet* 2000;**355**:39–40.
40. Morgenthaler TI, Kapur VK, Brown T, Swick TJ, Alessi C, Aurora RN, Boehlecke B, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep* 2007;**30**:1705–11.
41. Mitler MM, Hajdukovic R, Erman M, Koziol JA. Narcolepsy. *J Clin Neurophysiol* 1999;**7**:93–118.
42. Saletu B, Frey R, Krupka M, Anderer P, Grünberger J, Barbanoj MJ. Differential effects of a new central adrenergic agonist—modafinil—and D-amphetamine on sleep and early morning behaviour in young healthy volunteers. *Int J Clin Pharmacol Res* 1989;**9**:183–95.
43. Golicki D, Bala MM, Niewada M, Wierzbicka A. Modafinil for narcolepsy: systematic review and meta-analysis. *Med Sci Monit* 2010;**16**:RA177–86.
44. Robinson DM, Keating GM. Sodium oxybate: a review of its use in the management of narcolepsy. *CNS Drugs* 2007;**21**:337–54.
45. Fawcett J, Kravitz HM, Zajecka JM, Schaff MR. CNS stimulant potentiation of monoamine oxidase inhibitors in treatment-refractory depression. *J Clin Psychopharmacol* 1991;**11**:127–32.
46. Feighner JP, Herbstein J, Damlouji N, Combined MAOI. TCA, and direct stimulant therapy of treatment-resistant depression. *J Clin Psychiatry* 1985;**46**:206–9.
47. Ravindran AV, Kennedy SH, O'Donovan MC, Fallu A, Camacho F, Binder CE. Osmotic-release oral system methylphenidate augmentation of antidepressant monotherapy in major depressive disorder: results of a double-blind, randomized, placebo-controlled trial. *J Clin Psychiatr* 2008;**69**:87–94.
48. Fava M, Thase ME, DeBattista C, Doghramji K, Arora S, Hughes RJ. Modafinil augmentation of selective serotonin reuptake inhibitor therapy in MDD partial responders with persistent fatigue and sleepiness. *Ann Clin Psychiatry* 2007;**19**:153–9.
49. Greenway FL, Caruso MK. Safety of obesity drugs. *Expert Opin Drug Saf* 2005;**4**:1083–95.
50. Makris AP, Rush CR, Frederich RC, Kelly TH. Wake-promoting agents with different mechanisms of action: comparison of effects of modafinil and amphetamine on food intake and cardiovascular activity. *Appetite* 2004;**42**:185–95.
51. Lindenmayer JP, Nasrallah H, Pucci M, James S, Citrome L. A systematic review of psychostimulant treatment of negative symptoms of schizophrenia: challenges and therapeutic opportunities. *Schizophr Res* 2013;**147**:241–52.
52. Wittkampf LC, Arends J, Timmerman L, Lancel M. A review of modafinil and armodafinil as add-on therapy in antipsychotic-treated patients with schizophrenia. *Ther Adv Psychopharmacol* 2012;**2**:115–25.
53. Wagner GJ, Rabkin R. Effects of dextroamphetamine on depression and fatigue in men with HIV: a double-blind, placebo-controlled trial. *J Clin Psychiatry* 2000;**61**:436–40.
54. Breitbart W, Rosenfeld B, Kaim M, Funesti-Esch J. A randomized, double-blind, placebo-controlled trial of psychostimulants for the treatment of fatigue in ambulatory patients with human immunodeficiency virus disease. *Arch Intern Med* 2001;**161**:411–20.
55. Mendonça DA, Menezes K, Jog MS. Methylphenidate improves fatigue scores in Parkinson disease: a randomized controlled trial. *Mov Disord* 2007;**22**:2070–6.
56. Breitbart W, Alici Y. Psychostimulants for cancer-related fatigue. *J Natl Compr Canc Netw* 2010;**8**:933–42.
57. Ballon JS, Feifel D. A systematic review of modafinil: potential clinical uses and mechanisms of action. *J Clin Psychiatry* 2006;**67**:554–66.
58. Verrico CD, Haile CN, Newton TF, Kosten TR, De La Garza R. Pharmacotherapeutics for substance-use disorders: a focus on dopaminergic medications. *Expert Opin Investig Drugs* 2013;**22**:1549–68.
59. Napolitano E, Elovic EP, Qureshi AI. Pharmacological stimulant treatment of neurocognitive and functional deficits after traumatic and non-traumatic brain injury. *Med Sci Monit* 2005;**11**:212–20.
60. Chen RY, Cheng JY, Ko JS, Ng EM. Efficacy and safety of atomoxetine for attention-deficit/hyperactivity disorder in children and adolescents: meta-analysis and meta-regression analysis. *Psychopharmacology (Berl)* 2007;**194**:197–209.
61. Garnock-Jones KP, Keating GM. Atomoxetine: a review of its use in attention-deficit hyperactivity disorder in children and adolescents. *Paediatr Drugs* 2009;**11**:203–26.
62. Koda K, Ago Y, Cong Y, Kita Y, Takuma K, Matsuda T. Effects of acute and chronic administration of atomoxetine and methylphenidate on extracellular levels of noradrenaline, dopamine and serotonin in the prefrontal cortex and striatum of mice. *J Neurochem* 2010;**114**:259–70.
63. Pliszka S, AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2007;**46**:894–921.
64. Bangs ME, Tauscher-Wisniewski S, Polzer J, Zhang S, Acharya N, Desaiah D, Trzepacz PT, et al. Meta-analysis of suicide-related behavior events in patients treated with atomoxetine. *J Am Acad Child Adolesc Psychiatry* 2008;**47**:209–18.
65. Muir VJ, Perry CM. Guanfacine extended-release: in attention deficit hyperactivity disorder. *Drugs* 2010;**70**:1693–702.
66. Croxtall JD. Clonidine extended-release: in attention-deficit hyperactivity disorder. *Paediatr Drugs* 2011;**13**:329–36.
67. Scahill L. Alpha-2 adrenergic agonists in children with inattention, hyperactivity and impulsiveness. *CNS Drugs* 2009;**23**(Suppl. 1):43–9.

68. Arnsten AF. The use of α-2A adrenergic agonists for the treatment of attention-deficit/hyperactivity disorder. *Expert Rev Neurother* 2010;**10**:1595–605.
69. Shen WW. Stimulants and wakefulness-promoting agents. In: Shen WW, editor. *Clinical psychopharmacology for the 21st century*. 3rd ed. Taipei: Ho Chi Publishing Company; 2011. p. 403–38 [in Mandarin].
70. Cooper WO, Habel LA, Sox CM, Chan KA, Arbogast PG, Cheetham TC, Murray KT, et al. ADHD drugs and serious cardiovascular events in children and young adults. *N Engl J Med* 2011;**365**:1896–904.
71. Habel LA, Cooper WO, Sox CM, Chan KA, Fireman BH, Arbogast PG, Cheetham TC, et al. ADHD medications and risk of serious cardiovascular events in young and middle-aged adults. *JAMA* 2011;**306**:2673–83.
72. Fayyad J, De Graaf R, Kessler R, Alonso J, Angermeyer M, Demyttenaere K, De Girolamo G, et al. Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. *Br J Psychiatry* 2007;**190**:402–9.
73. Sattar S, Santosh PJ, Canagaratnam M. Efficacy and tolerability of pharmacotherapies for attention-deficit hyperactivity disorder in adults. *CNS Drugs* 2011;**25**:737–63.
74. Morein-Zamir S, Sahakian BJ. Neuroethical issues in cognitive enhancement. *J Psychopharmacol* 2011;**25**:197–204.
75. Greely H, Sahakian B, Harris J, Kessler RC, Gazzaniga M, Campbell P, Farah MJ. Towards responsible use of cognitive-enhancing drugs by the healthy. *Nature* 2008;**456**:702–5.
76. Glazer WM. In the pipeline: non-stimulant ADHD meds. *Behav Healthc* 2010;**30**:30–1.
77. Findling RL, Short EJ, Leskovec T, Townsend LD, Demeter CA, McNamara NK, Stansbrey RJ. Aripiprazole in children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2008;**18**:347–54.