

Smart Drugs: A Review

Sahjesh Soni, Dr Rashmi Srivastava, Ayush Bhandari

Mumbai Educational Trust, India

Abstracts

Smart drugs can change the way our mind functions. Smart drugs are also known as nootropics, which literally means the ability to bend or shape our mind. Smart drugs are classified into two main categories. They are classified based on their pharmacological action and their availability. The stimulant category of drugs is highly used and misused. There has been a rampant increase in the sale of smart drugs, which could be attributed to the rise in competition all over the world. Two major criteria for selecting a good drug are its mechanism of action and bioavailability. Owing to the short-term benefits of smart drugs, many countries have openly accepted this concept. There is still no concrete scientific evidence backing the safety and efficacy of these drugs. Some believe that this is just a fad that will soon pass, while others believe that this is something that will revolutionize our future.

Key Words: Smart drugs, Nootropics, Cognitive enhancers, Stimulants, Uses and Side effects.

What are Smart Drugs?

"Smart drugs" are a group of compounds that can promote brain performance. They have got a lot of attention due to our stressful lifestyle, and these drugs help to boost our memory, focus, creativity, intelligence, and motivation. The origin of the word comes from the Greek language meaning "to bend or shape the mind".¹

These chemicals have many mechanisms of action. Some of these mechanisms include improving blood flow, stimulating neurogenesis, and improving cell membrane fluidity. These actions create positive changes in the body, which help the body to function at 100% efficiency irrespective of the current state of the body.²

The examples of smart drugs are Caffeine (mostly used), L-theanine, Creatine, *Bacopa monnieri*, *Panax ginseng*, Nicotine, and Modafinil (most popular).¹

What are Nootropics?

Nootropics are non-prescription compounds and include a variety of substances, such as vitamins, herbs, which could improve cognitive ability and support peak performance.²

Difference between nootropics and smart drugs

Nootropics and smart drugs function in a very different manner. Nootropics facilitate the long-term strengthening of various brain regions by improving blood flow and oxygenation. Nootropics are

considered as super supplements. Nootropics are compounds that do not offer any side effects; the same is not true for smart drugs.³The examples of nootropics are Lions' Mane and Huperzine-A.³

Classification of Smart Drugs

Smart drugs can be classified in the following two ways:

1. Based on their availability
2. Based on their pharmacological action

1. Based on their availability

A. Prescription smart drugs: These drugs are psychostimulants that can be purchased only on a prescription. These drugs are used for patients with attention-deficit hyperactivity disorder (ADHD) and narcolepsy. In today's world, a lot of individuals used them as a way to enhance their ability to work and their attention span. The examples include Modafinil and Adderall.⁴

B. Over-the-counter smart drugs: These drugs can be purchased from ordinary retail stores. These drugs do not need a prescription or licensing as such. The examples include Caffeine and L-theanine.⁴

2. Based on their pharmacological action

On the basis of the pharmacological activity, smart drugs are divided into four groups, namely stimulants, racetams, cholinergic, and dopaminergic.⁴

A. Stimulants

These drugs are the most abused category of drugs. Their basic function is to make us feel more awake, alert, and focused, hence providing a boost of energy. These drugs have side effects that cannot be avoided, and hence, this category has built a bad name for them. On the other hand, some drugs are very useful and can be used to treat brain-related impairments. The examples are Modafinil and Adrafinil.⁴

B. Racetams

These drugs have a lot of evidence for their productivity. They function by fastening the chemical exchange between the brain cells. This process has a direct impact on our mental clarity and learning ability. These drugs are prescription drugs, for example, Piracetam.⁴

C. Cholinergics

These drugs affect the chemical acetylcholine, which in turn affects the peripheral nervous system. These drugs have a direct impact on our memory, mood, and attention span. Cholinergics are used with the racetam class of drugs, as the racetam class of drugs decreases our cholinergic levels also decrease. An example is Choline.⁴

D. Dopaminergics

These smart drugs are directly responsible for the release of the neurotransmitter dopamine. Dopamine makes us aware of our good feelings, and thus, gives us positive feedback. Moreover, our attention levels and alertness are improved by dopamine. The examples are Yohimbe and L-Deprenyl.⁴

Need for Smart Drugs

The immense pressure in jobs and the competitive environment in schools as well as colleges created the need for smart drugs. Students and professionals take these drugs because it seems as if it will provide them with an extra edge, and thus, help them with combating the pressure. Shockingly, the use of these drugs is accepted, and some students believe that these drugs increase memory and intelligence. Such claims have attracted a lot of students to try out and use these drugs. Most of them don't adhere to it, but there are some for whom it becomes a part of their lifestyle.⁵

These drugs have gained a lot of interest in professionals and tech startups. These individuals have claimed that these drugs increase their attention span and their ability to focus on the task at hand.

There is a set of professionals who are inclined to take these smart drugs. People who are at the higher managing post are likely to take these drugs more often. They take these drugs because their brain has to be active constantly. Their emotions cannot be driving their decision. These drugs help them in all their functions.⁵

These pills also help people make their decision faster than normal people. This is why it is an essential drug for military men, pilots, and astronauts.⁵ The drugs are also used by people who stay up all night for their professions, for example, surgeons, nurses, and DJs. A high level of concentration, stamina, attention, and energy is needed to accomplish such jobs. This is something provided by these smart drugs.⁵

People working as accountants, programmers, and PC analysts need to be accurate in every aspect of their job.⁵ This implies that they need to have the substantial mental capacity to be correct the entire time. Along with the mental capacity, they also require high concentration and the ability to hold one thought for long periods. These are the exact effects smart drugs provide; hence, its need has risen.⁵

Smart Drugs Used on Daily Basis

Smart Drugs	Uses	Side Effects
<p>Modafinil (Provigil) This drug possesses similar stimulating effects like cocaine albeit with less dependence. It is sold under the schedule IV category. It is mostly considered as non-addictive; however, reports of dependence and withdrawal have been noted. ^{6,7}</p>	<p>This drug is medicinally used to treat narcolepsy and sleep disorders.⁶ It also is used by many people to stay awake and improve focus and productivity.</p>	<p>The most common side effects are headache, nausea, nervousness, anxiety, insomnia, diarrhea, indigestion, back pain.</p>

<p>Adderall It is a prescription medication that contains two drugs, namely amphetamine and dextroamphetamine.⁸ It is available in two forms—the oral tablet form and the extended-release oral capsule form.¹⁰</p>	<p>This drug is used to treat ADHD and narcolepsy. It can increase the ability of an individual to pay attention and stay focused on an activity. The drug also has the ability to control behavior problems.¹²</p>	<p>This drug has a fair share of side effects, which include stomach ache, dry mouth, weight loss, and a decrease in libido.⁹⁻¹¹</p>
<p>Ritalin: It has the ability to cause hyperactivity, and quick impulses are sent to the brain. Its generic name is methylphenidate, and it goes by the brand name Methylin.¹³</p>	<p>Ritalin is used to treat patients with ADHD and narcolepsy.¹⁴It can increase attention span and decrease restlessness in children and adults.¹⁵</p>	<p>Ritalin has two kinds of side effects^{13, 14} More common side effects: Ones that do not need medical attention include headache, stomach pain, Less common side effects: Ones that need immediate medical attention include chest pain</p>
<p>Caffeine It is the most common stimulant used around the world.⁶ It was accidentally discovered by an Ethiopian shepherd. More than 85% of the world’s population consumes this product.</p>	<p>Caffeine is used for treating migraine when taken with aspirin. It is used to treat breathing problems in premature infants. Also, it is used to enhance mental alertness and reduce weight. It has also been proven to be useful in asthma.</p>	<p>Excess caffeine could lead to anxiety, irregular heart conditions, and weak bones (Caffeine can flush out calcium from the body through the urine).¹⁶</p>





Different dosage forms of caffeine
One of the most popular dosage forms of caffeine is bulletproof coffee. It is a high-calorie coffee that can replace our breakfast. It is rich in healthy saturated fats. Bulletproof coffee is known to impact metabolism, decrease weight, stabilize gut health, improve mood, and increase strength^{17, 18}.
Another form of intake of caffeine is caffeine tablets, which contain natural caffeine or artificial caffeine. It is known to provide a quick energy boost, reduce constipation, sharpen focus, and improve memory¹⁹.





<p>L-theanine It is an amino acid, which is found in tea leaves and mushrooms.²⁰ It is a source of umami, which has been known to stimulate metabolism, boost the sensation of fullness, and lengthen the time before another meal.²¹</p>	<p>L-theanine reduces anxiety and stress without any sedative effect. It reduces heart rate and blood pressure. It helps in improving mental performance and also helps people fall asleep quickly. ²⁰ It has applications in cancer.</p>	<p>It has side effects, namely nausea, upset stomach, and irritability. Additionally, it can lead to low blood pressure in cases having a history.</p>
<p>Ginkgo Biloba It is one of the top-selling herbal drugs. It is obtained from dried green leaves. It is available in capsule and tablet forms.²²</p> <p>Rhodiola It is native to the arctic region of Europe, Asia, and Alaska. The root is used as a medicine. It is called an adaptogen, as it adapts and resists stress.⁶</p>	<p>An extract of Ginkgo Biloba known as EGb 761 is used for Alzheimer’s dementia. It increases blood circulation, and hence, enhances memory. It also has uses in glaucoma.²²</p> <p>It is used to treat anxiety, anger, and confusion. Also, it is used to treat conditions, like irregular heartbeat and diabetes.²³</p>	<p>It may cause side effects, such as nausea, diarrhea, stomach ache, restlessness, and vomiting.²²</p> <p>The drug stimulates the immune system and worsens conditions, like multiple sclerosis and rheumatoid arthritis, and lowers blood pressure.²³</p>

<p>Omega-3 fatty acids Omega-3-fatty acids are found in fatty acids and fish oil supplements. They are polyunsaturated fats that enhance cognition.</p>	<p>Omega-3-fatty acids reduce the risk of heart disease and promote healthy skin. They are used to lower the levels of blood fats and raise the levels of good cholesterol. They are efficient in treating rheumatoid arthritis.^{24, 25}</p>	<p>Side effects include back pain, dry mouth, altered sense of taste.</p>
<p>Creatine It is found predominantly in muscle cells and helps the muscles produce energy while heavy lifting. Muscles store 95% of creatine as phosphocreatine, while the brain and the kidneys store 5%.²⁶</p>	<p>Its use leads to improved strength, power, and short-term muscle growth as well as long-term muscle growth. It can effectively treat conditions, namely epilepsy, Parkinson's disease, and Huntington's disease. Additionally, it also improves cell signaling and cell hydration.²⁶</p>	<p>Side effects of creatine include muscle cramping, stomach pain²⁶.</p>
<p>Memantine It has several additional uses such as to improve memory and awareness. It also can enhance the ability to perform daily actions.</p>	<p>This drug is used in the treatment of moderate-to-severe Alzheimer's disease. It can also be used in cases of hepatic impairment.²⁷</p>	<p>This drug has a lot of side effects, which include hypersensitivity, shortness of breath, hallucination, dizziness, irregular heartbeats, and tingling of hand.²⁷</p>

Mechanism of Action and Pharmacokinetics

Smart Drugs	Mechanism of Action	Pharmacokinetics
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<p>Modafinil</p>	<p>The drug binds to the dopamine reuptake pump.</p>  <p>Thus, the reuptake of dopamine is inhibited, and an increase is noted in extracellular dopamine.</p>  <p>The drug also causes indirect inhibition</p>	<p>The drug has rapid absorption and attains peak plasma in 2–4 hours.²⁹ It is well distributed in the body tissue. Its volume of distribution is larger than the volume of total body water.²⁹</p> <p>The liver is the major pathway of elimination by which 90% of the drug is eliminated.²⁹</p>
<p>Adderall</p>	<p>The drug promotes the release of dopamine and norepinephrine from the storage sites in the presynaptic neurons.</p>  <p>More dopamine and norepinephrine cause more stimulation. This leads to an increase in attention span, motivation, and memory.</p>	<p>The drug gets absorbed in the gut as it is a weak base. After 1–3 hours of oral administration and 15 minutes of injection, peak response for the same takes place. It shows bioavailability of over 75%.</p> <p>It is mainly excreted through the urine (90% in 3 days). The clearance rate is 0.7 L.h/kg.³⁰</p>
<p>Ritalin</p>	<p>The drug modulates and blocks the dopamine and norepinephrine transporter.</p>  <p>This increases the amount of available norepinephrine and dopamine, thus increasing their effects on the body.</p>	<p>The distribution is very low in the body. The drug is metabolized by de-esterification to alpha-phenyl piperidine acetic acid. After oral administration, 78% to 97% of the dose is excreted through the urine within 2–4 days.³¹</p>

<p>Memantine (Axura)</p>	<p>The drug blocks special types of receptors called N-Methyl-D-Aspartate (NMDA)</p> <p style="text-align: center;"></p> <p>This improves the transmission of signals in the brain, thus reducing the symptoms of Alzheimer's disease.</p>	<p>The drug possesses good absorption and has bioavailability of 100%. It has T_{max} of about 3–8 hours. Daily doses of 20 mg would achieve a steady concentration. The drug has $t_{1/2}$ of about 60–100 hours.³²</p>
<p>Caffeine</p>	<p>The drug acts as an antagonist binding to the adenosine receptors. Therefore, it blocks the adenosine receptors.</p> <p style="text-align: center;"></p> <p>It reduces the activity of adenosine receptors, which promote sleep in humans.</p> <p style="text-align: center;"></p> <p>Adenosine receptors also reduce the activity of dopamine and norepinephrine. Thus, by blocking the adenosine receptors, caffeine increases the activity of dopamine and norepinephrine.^{33, 34}</p>	<p>This drug takes 30 mins to 2 hours to reach peak concentration. Caffeine is rapidly distributed in the body tissues.³⁵</p> <p>The drug can cross the placenta and the blood-brain barrier. The peak plasma range for the drug is 6–10 mg/L.³⁶</p>
<p>L-theanine</p>	<p>After 20–30 mins of administration, theanine increases alpha brain waves, which take the brain into an alert yet a relaxed state.</p> <p style="text-align: center;"></p> <p>The drug also reduces beta waves, reducing excitability in the body.</p>	<p>First, the drug is absorbed in the gut and then into the blood-brain barrier. It takes approximately 1 hour for the onset of action³⁷.</p> <p>After intake of L-theanine in the form of capsule or tea, drug excretion occurs through the urine. A minor part of L-theanine is absorbed in the erythrocytes.³⁸</p>

Ginkgo Biloba	The drug is known to exert anti-inflammatory, antioxidant, cerebral glucose utilization, neurotransmitter regulation, and vasomotor actions. ³⁹	The maximum concentration of the drug is reported after 2.5 hours of drug administration. It can cross the blood-brain barrier and show its effect there. ⁴⁰
Rhodiola	It functions in two ways, which are interactions with the hypothalamic-pituitary-adrenal axis and influence on nitric oxide production. ⁴¹	The plasma concentration of the drug depends on the frequency of administration. It shows rapid absorption and elimination. Most of the drug excretion takes place through the urine. ⁴²
Omega-3 fatty acids	Omega-3 fatty acids lower the body's production of triglycerides. Omega-3 polyunsaturated fatty acids along with diet and exercise could lower the triglyceride level in the blood.	Omega-3 fatty acids are hydrolyzed in the intestinal lumen and incorporated into the bile salt. After which they are absorbed in the enterocytes by passive diffusion. Omega-3 fatty acids are metabolized and oxidized.
Creatine	The drug exerts its action by increasing phosphocreatine stores in the muscle. Thus, these additional stores could be used in producing extra ATP, which is then used as an energy source in lifting. ²⁶	The average half-life of the drug is four years. Half-life increases in patients with renal impairment. Major amount of the drug is eliminated by the kidney, and no reabsorption occurs. ⁴³

Smart Drugs Used by Different Countries

The number of individuals using smart drugs across the world has gone up drastically. The potential concern is that these drugs are not being used primarily for its medicinal effects. These drugs have other benefits that are being exploited by healthy individuals. These other benefits include memory enhancement or increase in concentration span. These benefits together are termed as pharmacological cognitive enhancement. The request for drugs like Ritalin and Adderall increased by 300% from 2015 to 2017.⁴⁴

In the period mentioned above, nearly 1/3rd of the population used the drugs for pharmacological cognitive enhancement only. The introduction of this drug created frenzy in a lot of developed countries in the world. Maximum units were sold in Europe in the year 2017, followed by the United Kingdom. The drug sales increased from a mere 3% to 16% in France.⁴⁴

There is a serious correlation between the increase in the sales of smart drugs in all developed countries with a high number of working hours. This is an indication of the prevalent competition that exists in such

countries. The question worth discussing—is using smart drugs ethical or is it cheating to others who do not use it?

These drugs originally aimed at treating diseases like ADHD. This line of treatment was introduced in the United States of America. Other countries with a higher number of patients for ADHD followed the same routine. The other countries include Canada and Australia.⁴⁴

This sudden rise of smart drugs points to the fact that people might be having problems with their working capacity and their social world rather than anything else. Many units of these drugs were sold through friends and word of mouth; 48% of people acquired the drug this way. Moreover, 10% of people bought through the internet, and only 4% had a prescription for the same.⁴⁴

Discussion

Many supplements are available at the present that claim to enhance our cognitive ability; however, several experts believe that these supplements do not increase our cognitive abilities unless taken for a very long time. Other reports claim that these supplements cannot compensate for natural food and provide health benefits.⁴⁵

Certain pharmaceutical preparations could increase our cognitive power and memory. The examples include Modafinil and Ritalin. Modafinil is a drug of superior effects and has proven pharmacological benefits. Though it has pharmacological benefits, it also has unwanted effects, such as headache, anxiety, and insomnia. Till date many drugs are termed as “SMART DRUGS,” but none of them have effectively proved to be safe in improving cognition.⁴⁵

The potential role of smart drugs is to increase the ability of people to do tasks which they would not do under normal circumstances. In layman’s terms, the effects of these drugs will ensure that people are focused for a longer period and work faster at their jobs. This does tend to extract a lot of work from an individual but is that what a “SMART DRUG” should do!

The most tapped in community of smart drugs is the stimulant type, which has escalated because of the rise in competition among people. It is true that right now almost anyone can apply for a job while sitting in any corner of the world.⁴⁶

Thus, people are going to an extreme extent to increase their efficiency. Other reports claim that smart drugs might alter the mechanism of the brain but do not increase the speed of the entire process.⁴⁶ A rough analogy for the same could be that you can’t accelerate an entire bus by just speeding its rear tires; all the tires and engine have to in sync for the bus to move fast.

It is certainly not easy to change the cognitive ability using these smart drugs and there is not much support in favour of using them.⁴⁷ Thus, it should be used when prescribed and in recommended quantities only.

Acknowledgement:

Authors would like to thank Mumbai Education Trust, Bhujbal Knowledge centre for their support. We would also like to acknowledge Dr. Neha Dave for her valuable inputs and corrections in the manuscripts.

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