

FACT SHEET: Stimulants

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What is a stimulant ?

A stimulant is any substance which increases or quickens a vital process. *Within* the central nervous system (brain and spinal cord), stimulants increase alertness, relieve fatigue, reverse cataplexy (muscle weakness), and/or induce euphoria. *Outside* the brain and spinal cord, stimulants frequently activate the sympathetic nervous system. Stimulation of this nerve highway prepares the body for “fight or flight” by dilating the pupils, increasing heart rate, and raising blood pressure.

How are drugs classified as stimulants ?

The World Health Organization characterizes pharmaceutical substances on the basis of three properties: chemical, pharmacological, and therapeutic. The *chemical properties* of a drug include molecular composition (of what atoms is it composed ?) and spatial conformation (how are its atoms arranged ?). Chemical properties can provide an important clue about what a drug will do within the body, because the shape of a molecule has profound implications for a compound’s net effect upon cellular processes (like a key fitting a lock).

Pharmacological properties refer to a drug’s effects upon discrete chemical systems, cell receptors, and intracellular processes. For example, many stimulants have direct effects upon dopamine and norepinephrine (catecholamines). Other stimulants, such as caffeine and nicotine, influence dopamine indirectly. The pharmacological features of stimulants include their effects upon the central and peripheral (autonomic) nervous systems.

The *therapeutic (e.g., behavioral) properties* of stimulants refer to heightened arousal, enhanced stamina (decreased need for sleep), feelings of well-being, and appetite suppression. Other common behavioral effects include nervousness, insomnia, agitation, mania, paranoia, hallucinations, and movement abnormalities (tics, dyskinesias).

What is the difference between stimulation and addiction ?

During the development of new drug products, chemicals are screened for potential addictiveness using non-human models (typically, mice and rats). An *addictive* compound refers to a chemical which rodents will self-administer – usually with increasing frequency, and sometimes to the point of starvation, sleeplessness, or death. This animal model is presumed to reflect the capacity of a substance to stimulate the “reward” centers of the brain, resulting in increased drug liking or wanting (craving).

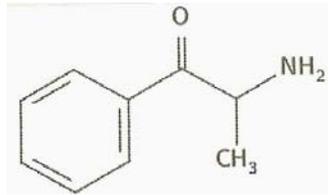
Under the Controlled Substances Act of 1970, addictive chemicals are designated by the Drug Enforcement Agency as “controlled” substances and ranked on one of five schedules (I through V) according to their relative propensity to induce compulsive use. It is possible for a pharmaceutical product to fulfill the criteria of a *stimulant* without meeting the DEA’s criteria for chemical addictiveness.

Despite marketing claims to the contrary, atomoxetine (Strattera) and bupropion (Wellbutrin, Zyban) are *non-controlled stimulants*. They have been marketed as **non-stimulants**, in order to avoid negative reactions by consumers who might otherwise reject their use because of the assumption that all stimulants are powerfully addictive.

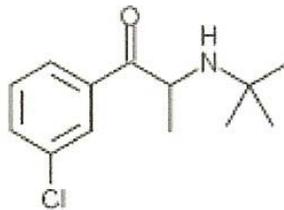
Examples of Stimulants That Have Been Marketed as Non-Stimulants

Bupropion (Wellbutrin) & Atomoxetine (Strattera)

Bupropion (Wellbutrin, Zyban) is *chemically* related to cathinone, the amphetamine ingredient of the botanical stimulant known as Khat or qat. As a substituted beta-keto-amphetamine, bupropion may trigger positive results on urine screens for illicit drug use.



chemical structure of cathinone

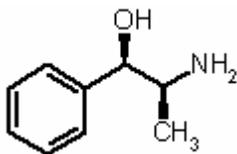


chemical structure of bupropion

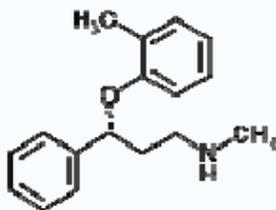
Bupropion's *pharmacological* effects include stimulation of the sympathetic nervous system (increase in heart rate and blood pressure), presumably via the modulation of catecholamines. Its usefulness in smoking cessation has historically been attributed to dopamine. However, more recent research has suggested a role for bupropion in blocking or antagonizing specific subtypes of cholinergic, nicotinic receptors on neurons.

Like other amphetamine compounds, bupropion's *behavioral effects* include anorexia, insomnia, arousal, agitation, mania, and psychosis.

Atomoxetine (Strattera) is a derivative of the stimulant *phenylpropanolamine*, or *PPA*. On November 6, 2000, the Food and Drug Administration issued a public health advisory about PPA, calling for its removal from over-the-counter cold remedies and other products due to its risk of hemorrhagic stroke (bleeding into the brain or surrounding tissues). It remains to be seen if atomoxetine will prove to have similarly dire effects upon the cerebrovascular system.



chemical structure of phenylpropanolamine



chemical structure of atomoxetine

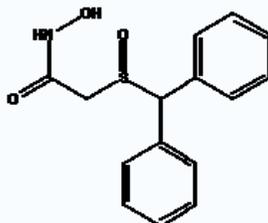
The direct *pharmacological effects* of atomoxetine involve the selective inhibition of the norepinephrine (adrenaline) reuptake transporter, a mechanism which is presumed to enhance the flow of noradrenergic signals in the brain and spinal cord. Peripheral actions include the stimulation of the sympathetic nervous system, leading to increased blood pressure and heart rate, dry mouth, mydriasis (pupillary dilation), and urinary retention or hesitancy.

Like other stimulants, atomoxetine is believed to enhance alertness by altering norepinephrine activity in the frontal cortex and brainstem. Other *behavioral effects* include insomnia, anorexia, nervousness, suicidality, hostility, akathisia, and mania.

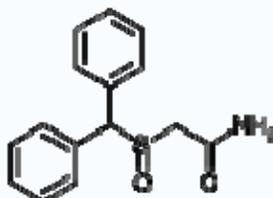
The fact that atomoxetine does not appear to enhance dopamine transmission in the striatum or the mesoaccumbens has encouraged some clinicians to suggest that atomoxetine is non-addictive. However, it should be noted that rats, pigeons, and monkeys have failed to distinguish between atomoxetine and low doses of cocaine or methamphetamine on drug discrimination tasks. Furthermore, the potential for atomoxetine to induce psychological rather than physiological dependence has not been systematically investigated or disproved.

What About Modafinil (Provigil, Sparlon) ?

Modafinil (Provigil, Sparlon) is classified by the World Health Organization as a centrally active stimulant with sympathomimetic effects. (This means that modafinil stimulates the sympathetic nervous system, increasing blood pressure and heart rate).



chemical structure of adrafinil



chemical structure of modafinil

Modafinil is a sulfinyl compound derived from adrafinil. The latter chemical is a central nervous system stimulant which was created in France in the late 1970s and subsequently tested as a treatment for narcolepsy.

The *pharmacological effects* of modafinil remain under investigation. Proposed mechanisms of action include the inhibition of dopamine reuptake (a feature shared by cocaine and methylphenidate), the activation of glutamate and orexin, the inhibition of GABA (a major inhibitory neurotransmitter), and the blockade of norepinephrine reuptake in the sleep promoting center of the brain.

The *behavioral effects* of modafinil qualify the drug as a super-stimulant. Originally approved by the FDA in 1998 as a treatment for narcolepsy, modafinil has been used by college students, shift workers, military pilots, and athletes to boost alertness, stamina, and wakefulness. Physicians have administered the drug to surgical patients to speed recovery from general anesthesia. The Drug Enforcement Agency classifies modafinil as a *controlled substance* (Schedule IV), based upon its potential for abuse. Rehabilitation centers have tested modafinil as a replacement for cocaine, and the International Olympic Committee has banned modafinil as an unauthorized, performance enhancing compound.

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