Chapter 6

CNS Stimulants: Use & Abuse

I love coffee, I love tea
I love the java jive and it loves me
Coffee and tea and the jivin' and me
A cup, a cup, a cup, a cup, a cup!
"Java Jive," 1940

The class of drugs designated as central nervous system (CNS) stimulants includes the two most frequently-used drugs on the planet, caffeine and nicotine. This chapter also includes all the amphetamines, cocaine, modafinil/Provigil, and the drugs approved to treat attention deficit hyperactivity disorder (ADHD) in children and adults, namely atomoxetine/Strattera, methylphenidate/Ritalin/Concerta/Daytrana, and the prodrug lisdexamfetamine/Vyvanse.

General Effects of Stimulants

All stimulant drugs cause an increase in general behavioral activity. When taken short-term (one or two weeks), stimulant drugs cause states of euphoria, optimism, and general feelings of well-being. Initial feelings of anorexia are frequent, a quality that leads to their use/abuse in weight loss products. Insomnia is also frequent. These responses indicate that the part of the brain which controls these functions, the hypothalamus, is strongly affected by these drugs and that the dopamine transmitter system is primarily involved in many of these effects. Other effects are:

- decreased feelings of depression
- increased thoughts and associations
- increased talkativeness • increased blood pressure
- anxiety • irritability • decreased fatigue

Tolerance to stimulants

Tolerance to the mood-elevating and appetite-suppressing effects develops after about two weeks of daily use. Little tolerance develops to the behavioral-arousal effect, which is what makes these drugs useful in the long-term treatment of narcolepsy (Stahl, 1999).

Abuse of Stimulants & Treatments for Withdrawal

A person who is addicted to stimulants, or who has had a long period of continuous use, will experience withdrawal symptoms if the drug is stopped abruptly. Symptoms of withdrawal from amphetamines and cocaine are very similar, mainly feelings of depression, fatigue, apathy, and general sluggishness, the opposite of the effects seen under the influence of these drugs. These symptoms, though not physically dangerous, can be very uncomfortable (Chiang & Goldfrank, 1990).

If a depressed person has been using stimulants on a long-term basis, has become dependent, or is abusing these drugs and increasing the dosage, then a severe depression may occur when the drug is withdrawn (Chiang & Goldfrank, 1990). If the depression caused by withdrawal does not abate after a week or two, evaluation by a psychiatrist for antidepressant medication is appropriate.

AMPHETAMINES

Amphetamine, dextroamphetamine, and methamphetamine (collectively referred to as "amphetamines") all have very similar properties and effects. The first amphetamine was synthesized in 1887, but it was not until the 1920s that it was investigated as a treatment for a wide variety of ills such as depression and nasal decongestion. In the 1930s, an inhaler, "Benzedrine" (mixed amphetamine sulfate), was sold over-the-counter and marketed for the treatment of asthma, hay fever, and the common cold. Methamphetamine (MA), discovered in 1919, is a crystalline powder that is easy to make (this is the "speed," "crank," or "meth" often made in illegal drug labs). It can be smoked, snorted, injected when dissolved in water, or taken in pill

form. During World War II, amphetamines were sometimes used to push soldiers to their limits, and even today "go pills" are used by U.S. military pilots to keep them awake when on long missions. Dextroamphetamine/Dexedrine and methamphetamine/Desoxyn were widely available in the 1950s and were popular with truck drivers and college students for staying awake, used by athletes to enhance performance, and taken and by millions as an appetite suppressant (Methamphetamine information, 2003).

Researchers may have discovered a reason why men have higher rates of addiction than women; male brains release up to three times more dopamine than female brains in response to amphetamine use. The men released between 50% and 200% more than the average females in the study. This may help explain the sex disparity in addictions (Munro, et al., 2006).

Methamphetamine addiction does destroy brain cells

In one study, high resolution MRI scans of methamphetamine addicts showed tissue destruction, particularly in gray matter. Losses were seen in the limbic region and the hippocampus. The study looked at 22 subjects who had used an average of four grams of methamphetamine per week for ten years, mostly by smoking it (Thompson, et al., 2004).

Psychological effects of methamphetamine use

Long-term users of methamphetamine frequently develop a variety of psychotic symptoms. These can be auditory hallucinations, paranoia, delusions, and formication (the illusion that insects are crawling on or under the skin) (Rawson & Ling, 2007).

Treatment of methamphetamine dependence

There are no FDA-approved drugs for methamphetamine dependence or withdrawal. A few currently in clinical trials are:

- Bupropion/Wellbutrin was shown to be somewhat helpful in increasing the number of drug-free weeks for low to moderate

methamphetamine users (Elkashef, et al., 2008).

- Mirtazapine/Remeron has shown promise for the treatment of withdrawal symptoms (McGregor, et al., 2005).
- Gamma-vinyl-GABA (GVG) (see p. 99) has shown some effectiveness keeping methamphetamine users drug free for at least four weeks. (Brodie, et al., 2005).
- Modafinil/Provigil was reported to decrease the severity of withdrawal symptoms. Subjects reported deeper sleep, fewer nightmares, and less sleepiness during the day (McGregor, et al., 2005).

All of these drugs may eventually prove to be helpful. However, larger, placebo-controlled trials are necessary to confirm their effectiveness.

Cocaine

Evidence suggests that the coca plant, *Erythroxylum coca,* was domesticated in South America around 1500 BCE. To this day, coca is an important part of many cultures in the Andes, where it is used in social rituals and its leaves are chewed to provide stimulation and relief from hunger. The plant's active ingredient, cocaine, was isolated by chemists in 1860. In the latter half of the 19th century, cocaine was considered to be an elixir, and was included in many patent medicines.

Coca-Cola®, which takes its name from the coca plant, included cocaine as an ingredient when it was introduced in 1885, which helped to make Coke® the world's most popular soft drink. The cocaine was removed in 1903 as its dangers began to be recognized (Krol, 2003).

Cocaine ("coke," "crack") is a potent CNS stimulant which is biochemically similar to the amphetamines and produces similar (although shorter-lasting) mood-elevating effects. The behavioral effects of cocaine are also similar to those of the amphetamines. Various formulations of cocaine (Novocaine, Lidocaine, Carbocaine, etc.) have been used as local anesthetics for many years.

Cocaine can be lethal, particularly if taken by injection. Fatality

can result from heart failure, respiratory depression, stroke, or seizures (Chiang, & Goldfrank, 1990). People have been known to die the first time they try cocaine, usually from previously unknown heart defects.

Brompton's cocktail

Brompton's cocktail is a medicinal concoction of cocaine, methadone, and alcohol. It is used with terminally-ill patients to alleviate extreme pain. The cocaine counteracts the sedation caused by the methadone. Brompton's cocktail is not used more generally because it has the potential to be highly addictive due to the rapid onset of stimulant and euphoric effects (McGiverny & Crooks, 1984).

Psychotic symptoms in cocaine users

In terms of psychological effects, cocaine use can produce a psychosis that is indistinguishable from the psychosis seen with paranoid schizophrenia. The best way to distinguish between these is either to run a blood test for cocaine, or wait until the drug should have worn off and see if the psychotic symptoms abate.

A treatment dilemma may occur if a cocaine user is also having psychotic symptoms and needs to be treated with an antipsychotic drug. Administration of antipsychotic drugs leads to increased cravings for cocaine. This is probably due to the blocking of dopamine receptors caused by the antipsychotic medication. The cravings may lead to an increase in cocaine use, which then may lead to a worsening of psychotic symptoms (Chiang & Goldfrank, 1990).

Treatments for Cocaine Dependence

Currently there are no FDA approved medications for treatment of cocaine dependence. Some drugs that are currently undergoing clinical trials are discussed below. All of the proposed mechanisms of action for these drugs are very hypothetical.

Gamma-vinyl-GABA (GVG)

GVG is an antiepileptic drug which has been shown to reduce cocaine

cravings. It is believed to work by enhancing GABA transmission in the CNS. The usual side effects are sleepiness and fatigue. It is not approved for use in the U.S. but it is available in Canada and other countries (Gerasimov, et al., 2000; Peng, et al., 2008).

Disulfiram

Disulfiram/Antabuse has been evaluated as a treatment for individuals with comorbid alcohol and cocaine abuse. Disulfiram-treated subjects decreased the quantity and frequency of their cocaine use significantly more than those treated with placebo (Petrakis, et al., 2000). The specific mechanism for this effect is not yet clear (Kampman, 2005).

Gabapentin

Gabapentin/Neurontin is an antiepileptic drug which appears to be safe and effective in reducing cocaine usage. Gabapentin is hypothesized to reduce cocaine use by its action on GABA and dopamine pathways in the brain (Raby & Coomaraswamy, 2004).

Topiramate

Topiramate/Topamax may help with relapse prevention due to its effects on both GABA and glutamate neurotransmission. Topiramate increases cerebral levels and facilitates neurotransmission of GABA (Kuzniecky, et al., 1998, Petroff, et al., 1999). Topiramate also inhibits glutamate neurotransmission (Gibbs, et al., 2000).

Modafinil

One study compared the use of cognitive-behavioral therapy to a combination of cognitive-behavioral therapy and modafinil/Provigil with subjects in recovery from cocaine use. Those subjects receiving both modafinil and CBT were more likely to remain cocaine-free than those receiving CBT alone (Dackis, et al., 2003). Modafinil may work by ameliorating glutamate depletion seen in chronic cocaine users (Dackis, et al., 2005).

Cocaine vaccine

A vaccine is being tested that induces the formation of anticocaine antibodies. The antibodies combine with cocaine to form a large molecular complex which has difficulty crossing the blood-brain barrier; this leads to a decrease in the amount of cocaine that penetrates the brain. The impact on the pleasure centers is greatly diminished if only a small amount of cocaine gets into the brain. In animal models, addiction was extinguished using these methods. The anticocaine antibodies remain in the blood and are effective for six months to one year, after which time booster shots might be required.

One danger with this treatment is that very large doses of cocaine might be able to overcome the antibodies which could lead to a lethal overdose. If effective, it is hoped that the vaccine will be a valuable adjunct to psychotherapy for cocaine users who want to overcome their addiction (Orson, et al., 2008; Sussman, 1997).

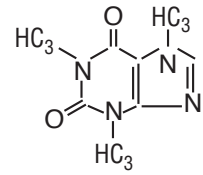
Relapse Prevention therapy/Harm-Reduction model

Relapse Prevention therapy (RP) (also known as the Harm-Reduction model) is one of the few scientifically validated psychosocial treatments for substance abuse that has been proven useful for treatment of cocaine abuse. No other type of currently available treatment is without major difficulties or side effects. RP techniques help people recognize high-risk situations, rehearse ways to deal with them, self-monitor substance use, and learn to deal with cravings by understanding and discussing them.

With this type of therapy, lapses in behavior are regarded as learning tools (i.e., ways to understand what happened) as well as opportunities to renew the commitment to sobriety. RP does not result in greater total abstinence rates than other treatments, but relapses are shorter. RP may be better in the long term for maintaining a lower relapse rate (Carpenter, 2001; Foxhall, 2001).

Caffeine

Coffee and tea are the most common sources of caffeine. Tea is made from the leaves of the *Camellia sinensis* plant and is believed to have been in use in China since about 2700 BCE. The legend is that a servant of the emperor was boiling water when the leaf of an overhead tree dropped into the water, and the emperor decided to taste it (Golender & Bouquet, 2003). He must have liked it.



$(C_8H_{10}N_4O_2)$
caffeine

Fig. 6.1

Coffee is made from the berries of species of the genus *Coffea*, in particular *Coffea arabica* and *Coffea canephora.* One legend says that its stimulant property was discovered by a shepherd who observed his flock becoming hyperactive after eating the bright red berries. Coffee has been consumed as a beverage in Middle Eastern cultures since about 1100 CE. When it was introduced to Europe in about 1600, many considered it the "devil's drink" because it was popular in non-Christian societies. Then the pope tried it, and he liked it so much he "baptized" it, thereby removing its stigma (The coffee plant, 2003).

Caffeine is the most widely-used psychoactive substance. Eighty-nine percent of adults in the U.S. use a caffeinated beverage daily. The average user consumes approximately 1,000 cups per year (about three cups per day). Most people do not think of it as a drug, but caffeine is a powerful stimulant. Although its use is legal, overdosing on caffeine, though it might be difficult (more than 5 to 10 grams at one time), can be fatal. Caffeine is quite addicting; tolerance and a tendency to increase intake are common, and withdrawal symptoms will occur if consumption is stopped (Hughes, et al., 1991).

Because caffeine makes people feel better in general, it is often included as an ingredient in analgesics (e.g., Anacin, Excedrin) as well as in many cold preparations. Caffeine intake can be estimated using Table 6.1 (amounts are approximate, and the caffeine content will vary depending on the product and the method of preparation).

Effects of caffeine

Caffeine causes an increase in cellular activity in the CNS and behavioral and emotional responses that are similar to, but milder than, the amphetamines and cocaine. After consuming caffeine, people report thinking more clearly, having more energy, and having faster reaction times (Hughes, et al., 1991). Increases are seen in respiratory rate, amplitude of reflexes, and the rate and force of the heart's contractions (systolic blood pressure). The stimulating effects of caffeine can take up to 12 hours to wear off. Caffeine use contributes significantly to problems with sleep.

Caffeine Content

SOURCE	SERVING	CAFFEINE (mg)
coffee (drip)	8 oz.	175–240
coffee (perked)	8 oz.	100–200
coffee (instant)	8 oz.	65–170
coffee (decaffeinated)	8 oz.	3–8
black tea (steeped 5 min.)	8 oz.	65–160
green tea (steeped 5 min.)	8 oz.	80
hot cocoa	8 oz.	3–16
cola beverages	12 oz.	45
"energy" beverages	8 oz.	80
milk chocolate	1 oz.	1–15
bittersweet chocolate	1 oz.	3–35
chocolate cake	1 slice	20–30
Anacin, Midol	2 tablets	64
Excedrin	2 tablets	130
NoDoz	2 tablets	200
Dexatrim	2 tablets	200

* Food & beverage contents approximate. Table 6.1

Caffeine causes a general *vasodilatation* (opening) of the systemic blood vessels, including the coronary arteries, resulting in an increase in blood flow to the heart. The duration of systemic vasodilatation is brief and is accompanied by a *vasoconstriction* (tightening) of the vessels in the brain (Hughes, et al., 1991). Central vasoconstriction is the mechanism by which caffeine provides relief from both hypertensive and migraine headaches. This is another reason why caffeine is often found in headache remedies.

Caffeine dependence

People who are caffeine-dependent have a strong association between caffeine consumption and feelings of well-being. Many people enjoy the increased speed of performance and feelings of

efficiency and mental clarity caused by caffeine. Regular caffeine consumption causes both psychological dependence and physiological tolerance (Hughes, et al., 1991).

Caffeinism

This disorder is a chronic toxicity caused by very high levels of caffeine consumption. It is characterized by:

- disruption of sleep patterns
- nausea
- diarrhea
- headache
- trembling
- dry mouth
- rapid changes in mood
- depression
- stomach pain
- feelings of anxiety
- ringing in the ears
- irregular heartbeat
- palpitations

Caffeine withdrawal

The main symptom of caffeine withdrawal is headaches; if no caffeine is consumed these may continue for up to five days. The headaches often lead to use of analgesic preparations which may contain caffeine. This will cure the headache but lead to a continuance of caffeine dependence. Other symptoms of withdrawal are:

- apathy
- irritability
- restlessness
- decreased efficiency
- lethargy
- mild nausea
- nervousness
- difficulty concentrating

It is possible to reduce withdrawal symptoms by gradually decreasing the daily intake of caffeine by substituting decaffeinated coffee or tea and increasing the percentage of decaf each day.

Other Effects of Caffeine, Pros and Cons

Liver cancer

A study of more than 90,000 Japanese found that those who drank coffee every day, or nearly every day, had approximately half of the risk of contracting liver cancer than people who never drank

coffee. The effect was seen in people who drank one to two cups of coffee per day and increased at three to four cups. This study was done at the National Cancer Center in Tokyo and was reported in the *Journal of the National Cancer Institute*. There was no association found between drinking green tea and liver cancer rates (Inoue, 2005)

Diabetes

One study that looked at the amount of coffee and tea consumed by 126,000 people over a 12-18 year period found that drinking more than four cups of caffeinated coffee per day reduced the risk of type 2 diabetes in men by about 50% and in women by about 30%. Drinking decaf resulted in a more modest effect, a 25% reduction in men and 15% in women. These data suggest that long-term coffee consumption is associated with a statistically significantly lower risk for type 2 diabetes (Salazar-Martinez, et al., 2004).

Heart disease and inflammatory disease

A fifteen year-long study was done with 27,312 women ages 55-69 who had not been diagnosed with heart disease, diabetes or cancer. Women who drank one to three cups of coffee daily were 24% less likely to die of heart disease compared with those who did not drink coffee. The coffee drinkers were also 28% less likely to die of other non-cancerous inflammatory diseases. Cancer deaths did not show any correlation with coffee consumption (Anderson, 2006).

Caffeine and cognitive decline

A study of cognitive decline looked at 4,179 women and 2,820 men (mean age 74), all of whom did not have dementia. After four years, the men had a normal age-related decline, but the women who drank at least three cups of coffee per day did not have a decline in verbal and visio-spatial memory. The overall risk of dementia was not related to the amount of caffeine consumed (Ritchie, et al., 2007).

Birth defects

Even though no significant correlation between birth defects and

caffeine consumption has been demonstrated (Browne, 2006), it is important for women to know that caffeine crosses the placenta and gets into the bloodstream of a developing fetus. It also gets into the breast milk of nursing mothers. In both cases, the fetus or infant is ingesting a portion of the caffeine consumed by its mother.

Low birth weight infants

Maternal third-trimester serum paraxanthine concentration (which reflects caffeine consumption) was measured. Higher levels were associated with an increased risk of reduced fetal growth, particularly among women who smoked (Klebanoff et al., 2002).

Miscarriage

When pregnant women who did not consume caffeine were compared to pregnant women who did, the risk of miscarriage increased in direct proportion to the daily dose of caffeine consumed. In addition, the magnitude of the association appeared to be stronger among women without a history of miscarriage than among women with such a history (Weng, et al., 2008).

Bone loss

Daily consumption of more caffeine than the amount in about two to three servings of brewed coffee may accelerate bone loss from the spine and total body. This effect was seen only in women whose calcium intakes were below the recommended daily allowance (RDA) of 800 mg (Harris & Dawson-Hughes, 1994).

Fibrocystic breast disease

There seems to be a relationship between caffeine and *fibrocystic breast disease*. The specifics are not yet clearly understood (Hughes, et al., 1991). Decreasing caffeine consumption leads to a decrease in discomfort experienced by women with this disease. Although many studies have been done with large numbers of adults, and no correlation between caffeine consumption and breast cancer has been substantiated.

Effects of age and tobacco use on caffeine metabolism

A person's age will usually affect his or her physiological response to caffeine. Most people become more sensitive to caffeine's effects as they get older. It has also been observed that the amount of caffeine in the bloodstream increases when tobacco smoking is stopped. This increase in the blood level of caffeine can amplify the effects of nicotine withdrawal, such as irritability, nervousness, an inability to concentrate, and sleeplessness.

Anxiety

Studies show a positive correlation between caffeine use and anxiety disorders. People with anxiety disorders have an increased sensitivity to caffeine (Charney, et al., 1985). Symptoms of anxiety decrease with caffeine abstention, and for some people antianxiety medication is not necessary if caffeine use is discontinued (Bruce & Lader, 1989). The psychotherapist needs to assess caffeine intake in any patient who presents with symptoms of anxiety. In some individuals, reducing caffeine intake will eliminate the anxiety.

NICOTINE

The source of nicotine is the tobacco plant, *Nicotiana tabacum,* which is native to the western hemisphere. Tobacco was in use by indigenous peoples when the first explorers arrived from Europe, and its use quickly spread to the Old World (Borio, 2003). Today, nicotine is widely used in almost every country.

According to the Center for Disease Control and Prevention's 2004 report, about 23% of American adults (about 50 million people) use tobacco products. Although nicotine is extremely addictive and known to be harmful, its purchase and use by anyone over the age of 18 is legal. If one considers how difficult it is to stop using it, nicotine is even more addictive than opioids. Using nicotine, particularly through smoking, is much more harmful than using many other legal drugs in terms of the number of illnesses smoking causes, the costs of treating those illnesses, and the high fatality rates among habitual users.

Antismoking campaigns in the U.S. have lowered smoking rates, but there has been an increase in the percentage of people worldwide who smoke. It is estimated there are more than 440,000 smoking-related deaths every year in the U.S. alone (Longley, 2005). Although nicotine is the ingredient that causes physical dependency, it is the "tars" (the resinous, partially-combusted particulate matter produced by the burning of tobacco) that contain most carcinogens.

Nicotine and mood

Nicotine consumption causes the release of norepinephrine, dopamine, and serotonin in the CNS. This leads to feelings of both stimulation and decreased reactivity. Research indicates that part of the calming effect smokers experience is due to the decrease in the unpleasant withdrawal symptoms habitual users experience as nicotine levels in the blood drop. When nonsmokers or former smokers are compared to current smokers, indications are that nicotine is not calming but is actually a stimulant (Parrott, 1999).

It is now thought that nicotine withdrawal itself does not increase baseline anxiety. Rather, it is the response to stressors during withdrawal that is heightened (Jonkman, et al., 2008). This research supports the belief that relapse of smoking behaviors will be greater in people who are subjected to greater external stress. It follows that calming activities like meditation and yoga may support abstinence from nicotine.

Nicotine addiction and major mental illnesses

The release of DA is probably what leads to the reinforcing experience of pleasure associated with tobacco use (this release of DA is similar to that observed with other addictive drugs). Nicotine has a half-life of 30 minutes, which leads to an urge to consume more nicotine every half hour. Two cigarettes an hour (or the equivalent form of other tobacco products) will maintain a constant level of nicotine in the blood.

For reasons that are not yet clear, about 10% of smokers do not

become addicted. They are able to keep consumption of cigarettes to approximately five per day, as opposed to the one or two packs a day consumed by the addict (Breslau, et al., 1991).

Tobacco leaf
Nicotiana tabacum

Recent research on cocaine may help to explain why some people become addicted to nicotine while others do not (Lohoff, et al., 2008). Genetic differences have been found between people who become dependent upon cocaine and those who remain casual users. Results suggest that variation in an enzyme, catechol-O-methyl transferase (COMT), which breaks down NE, 5-HT and DA, is related to the risk of dependency (Lohoff, et al., 2008). Similarly, genetic differences may explain why some people become dependant on nicotine.

People addicted to nicotine have higher rates of major depression and anxiety disorders than those who smoke but are not addicted (Walton, et al., 2001). One study found that 90% of people who attempt suicide are smokers (Leistikow, et al., 1996). More research is needed to analyze the factors responsible for these findings.

It is estimated that about 70% of people with schizophrenia smoke, a much higher percentage than in the general population. There is evidence that cigarette smoking ameliorates the unpleasant symptoms caused by schizophrenia and by antipsychotic medication. The harm-reduction approach combined with the nicotine patch or nicotine gum, is the recommended treatment for decreasing smoking in this population (McChargue, et al., 2003).

Smoking associated with cognitive decline

Using the Mini-Mental Status Exam, researchers examined changes in cognition over 2 1/2 years in 9,209 people over age 65 who did not have dementia. They found that a higher pack-per-year smoking exposure was associated with a greater decline in cognition (Ott, et al., 2004).

Tars & other compounds found in tobacco products

Some known carcinogens found in tobacco tars include:

- benzopyrenes
- pyrenes
- aromatic amines
- chrysenes
- nitrosamines

There are many other substances known to be harmful to humans that are frequently present in tobacco products, including:

- cresols
- phenols
- metallic ions
- radioactive compounds
- carboxylic acids
- various additives and flavoring agents
- agricultural compounds (e.g., pesticides)

If manufacturers removed these toxic agents from their products the harmful effects of tobacco use would be greatly reduced.

Nicotine withdrawal

Physiological symptoms of withdrawal occur when someone who is addicted to nicotine stops consuming it. This withdrawal syndrome is commonly called a "nicotine fit." Symptoms of withdrawal are:

- anxiety
- headache
- restlessness
- nervousness
- feelings of uneasiness
- digestive disturbances
- impairment of psychomotor performance
- impairment of concentration and judgement

When the body is under stress, nicotine is depleted faster than usual, causing the addict to increase consumption in order to maintain the usual blood-level of nicotine and prevent withdrawal symptoms.

Treatments for Nicotine Withdrawal

Patches, gums, lozenges & inhalers for nicotine withdrawal

The nicotine patch, nicotine gum, nicotine lozenges, or a nicotine inhaler are all useful for helping people to decrease and quit tobacco use. Simply trying to "cut down" on smoking continues to expose the individual to the health risks and reinforcing behaviors inherent in tobacco use. These products all contain nicotine and are addictive but

decrease the major health risks caused by inhaling smoke and permit tapered nicotine withdrawal. They also help to break behavioral patterns associated with tobacco use.

Bupropion & naltrexone for nicotine withdrawal

The FDA's Drug Abuse Advisory Council found that the antidepressant bupropion/Wellbutrin/Zyban is safe and effective as an aid in smoking cessation (Jorenby, et al., 1999). Another drug, naltrexone/Revia (developed for use during opioid withdrawal), has been found to decrease the craving for nicotine (Ahmadi, et al., 2003). Both of these drugs are useful as supportive measures in addition to psychotherapy, especially in the early stages of abstinence.

Varenicline tartrate

Varenicline/Chantix was approved by the FDA as an aid to smoking cessation treatment in May 2006. It is believed to work by blocking the stimulating and dopamine-releasing effects that occur when nicotine is consumed (Naiura, et al., 2006).

Black box warning

In 2008, the FDA announced that the connection between Chantix and serious psychiatric problems was increasingly likely. In 2009, the agency required that Chantix and another smoking-cessation drug, Zyban, carry the FDA's strongest safety warning regarding possible side effects (including depression and suicidal thoughts).

Clonidine for nicotine withdrawal

Another drug that may be helpful during nicotine withdrawal is clonidine/Catapres. Clonidine is an antihypertensive drug that has shown evidence of decreasing cravings during nicotine withdrawal (Ahmadi, et al., 2003; Gourlay, et al., 1994). Clonidine is not FDA-approved as a treatment for nicotine withdrawal.

Nicotine vaccine

The effect of immunization against nicotine was studied in anesthetized rats (Hieda, et al., 1999). Results found nicotine-specific

antibodies and a reduction of the nicotine in the brain. These data suggested that the use of immunization of humans to modify the effects of nicotine may be possible.

Nic Vax (a nicotine vaccine) is now in Phase III human trials, and so far it seems to be both safe and effective, although the response rates seen are not better than those achieved by other available methods. This research suggests that the vaccine may be more useful for preventing relapse rather than for smoking cessation (Hatsukami, et al., 2005).

Effect of caffeine during nicotine withdrawal

Caffeine is metabolized more quickly by smokers than by nonsmokers. If someone stops using nicotine, and the amount of caffeine consumed remains constant, the level of caffeine in the blood will double. This will cause an increase in nervousness that makes withdrawal from nicotine even more difficult. For this reason, it is recommended that caffeine consumption be decreased or eliminated during withdrawal from nicotine (Bruce & Lader, 1989).

Attention Deficit Hyperactivity Disorder (ADHD)

Using the *DSM* definition, the prevalence of attention deficit hyperactivity disorder (ADHD) in the U.S. is between 8% and 16%. Boys are four times more likely to be given this diagnosis than are girls (Wender, 2002). Although there is much overlap between the symptoms of ADHD and childhood bipolar disorder, one difference is that children with ADHD still have a normal need for sleep, whereas children with bipolar disorder will not require normal amounts of sleep (John Preston, MD, personal communication, 8/26/06).

Genetic findings

There is strong evidence for a genetic component in ADHD. Twin studies show a 65-95% concordance rate. This is comparable to rates in schizophrenia and bipolar disorder (Brown, 2003).

Anatomical differences in brain scans of children with ADHD

Anatomical differences have been found in scans of areas of the brain which control communication in children diagnosed with ADHD. They found that these differences diminished in children who had been medicated with stimulant drugs for an average of 2 1/2 years (Ashtari & Kumra, 2004).

Treatments for ADHD

Amphetamines & methylphenidate

Methylphenidate was synthesized in the 1940s and marketed under the brand name Ritalin in the 1960s (History of methylphenidate, 2003). In the U.S. alone, about 11 million prescriptions are written every year for methylphenidate (now including Concerta and Focalin) and another six million are written for various amphetamine compounds such as Adderall (DEA Congressional Testimony, 2000). These drugs are useful in decreasing hyperactive behavior in both children and adults. The mechanism for the paradoxical response in these populations (i.e., why taking a stimulant results in calming) is not yet fully understood (Gainetdinov, et al., 1999).

When taking methylphenidate, children who were previously unable to concentrate and had difficulty learning were able to perform at their age-appropriate level. Tolerance and dependence do not develop in children who are taking these medications. A slowing of growth has been observed when children take methylphenidate for long periods. This may be due to the appetite-suppressing side effect. To remedy this, children are given "drug vacations" from their medication on weekends and/or over the summer when they are not in school. This break usually allows children time to catch up on their growth if it had slowed due to the medication.

Methylphenidate and amphetamine can be drugs of abuse. They can be snorted or dissolved and then injected for a rapid effect (drug "rush"). When used in this manner, they have effects like cocaine, but milder. A tolerance will develop if they are used frequently in this way,

and withdrawal symptoms will occur if one stops taking the drug (Chiang & Goldfrank, 1990).

Lisdexamfetamine dimesylate

Because of problems of abuse, a new formulation called a "prodrug" has been developed for the treatment of ADHD. This prodrug, lisdexamfetamine dimesylate/Vyvanse, is converted to an active compound in the liver. Because it does not become active until it is metabolized, it is less likely to be abused.

Guanfacine

Guanfacine/Intuniv was approved by the FDA in September 2009 for the treatment of ADHD in children and adolescents ages six to 17. It is thought to work by engaging NE receptors in the prefrontal cortex to improve memory, attention regulation, impulse control, and to decrease susceptibility to distraction (Waknine, 2009).

Atomoxetine

The drug atomoxetine/Strattera is the only FDA-approved treatment for ADHD in adults as well as in children. This drug is not officially considered a stimulant because it is believed to work more on NE than DA. For this reason it is not a controlled substance, so more doctors are willing to prescribe it. A major advantage of this medication is that it only needs to be taken once in the morning and its effect lasts until evening without causing insomnia. A 13-item diary was developed by the manufacturer so that parents could assess efficacy of the drug on their children. The symptoms evaluated included:

- oppositionality
- hyperactivity/impulsivity
- inattentiveness/distractibility
- inability to concentrate on structured tasks

Children were rated during the early morning and in the evening. According to parent ratings, atomoxetine was found to be effective in alleviating these symptoms (Michaelson, et al., 2003).

There are indications that reducing the dose of atomoxetine may be necessary for patients with impaired liver functions (Chalon, 2003). The FDA now requires a "black box" warning for this drug. The warning states that atomoxetine may increase the incidence of suicidal thinking in children and adolescents.

Cardiac risks with stimulants

In 2008, the American Heart Association issued guidelines recommending an electrocardiogram (ECG) as part of the medical workup for children and adolescents before starting them on ADHD medication. The American Academy of Pediatrics responded that there was no evidence that doing this would balance issues of risk, benefit, and cost-effectiveness in identifying risk factors for sudden death in children being treated with stimulants; therefore, an ECG was not warranted. The consensus reached was to call for "careful assessment" for heart conditions in children being considered for ADHD medication. This would include a physical examination and an in-depth family history to assess for risk factors and cardiac problems. The child's physician would then determine whether an ECG was appropriate. The risk of sudden cardiac death from these medications is about the same as the risk from participating in strenuous exercise (American Academy of Pediatrics, 2008).

Buspirone

Although developed as an antianxiety medication and not considered a stimulant, buspirone/Buspar has been found to be as effective as methylphenidate/Ritalin in reducing symptoms of ADHD, with minimal adverse effects. Some children experienced dizziness during the first week on buspirone (Malhotra & Santosh, 1998).

Caffeine & ADHD

Caffeine has been shown to improve functioning and reduce levels of hyperactivity in children with ADHD. Although traditional treatments with methylphenidate and amphetamines outperform caffeine in improving functioning, caffeine outperforms the control

groups getting no treatment. Some improvements are:

- better relationships with parents and teachers
- reduced aggression
- improved executive functioning
- reduced hyperactivity
- reduced impulsiveness (Chalon, 2003)

This evidence indicates that caffeine is helpful for children with ADHD and may be valuable as an alternative to the more potent stimulants (O'Connor, 2001). Opinions differ on whether caffeine use in children is harmful. No long-term studies have been done to assess its effects on physical and psychological functioning in children. Most children respond to caffeine in the same way as adults. There is a stimulating effect, observed as nervousness, and when tested, response time is shortened (O'Connor, 2001).

Caffeine may be an option for parents who are opposed to the use of other stimulants. This may ease their fears of the adverse effects on their children from the long-term use of more powerful stimulants.

ADHD and substance abuse

Parents are frequently concerned that treating their children with stimulants will increase the risk of substance abuse in the future. Many studies have been done to investigate this issue. In a meta-analysis of results from six studies where subjects were followed from four years old to adolescence and then to young adulthood, it was found that the risk of substance abuse was about half for the youths who were treated with stimulants as compared to youths who were not medicated for their ADHD. The risk reduction was similar when both alcohol abuse and drug abuse were evaluated (Wagner, 2004).

Stimulants for Treatment of Depression

The amphetamines and methylphenidate may be appropriate for short-term use to treat depression, but due to fears of their addictive potential, they are not frequently prescribed (Wagner, et al., 1997). Even the caffeine in coffee and tea will usually improve mood.

Stimulants can be useful for treating depression when apathy and lack of motivation are present. These drugs can help to get someone launched on a regime of exercise and constructive activities that may help to maintain an elevated mood. Their virtue is that as stimulants they act immediately, whereas most antidepressants take several weeks to reach their maximal effect. Immediacy can be critical if a patient is suicidal. It is this immediacy of response which also makes stimulants potential drugs of abuse. People who have no history of addiction usually do not become addicted when taking these drugs for therapeutic purposes (Satel & Nelson, 1989).

Direct Relevance to Psychotherapy

It is very important to be aware that a paranoid psychosis may result from long-term use of stimulant drugs (particularly with amphetamines or cocaine). This drug-related condition may be clinically indistinguishable from the paranoid psychosis seen with schizophrenia or during a manic episode. The symptoms may include: hostility, paranoia, delusions, aggressiveness, disorganized thought patterns, and hallucinations (usually auditory). These psychotic symptoms occur most often when there is a sudden increase in dosage, or in chronic users of amphetamines who are taking more than 100 mg/day.

The treatment of choice for this drug-induced psychosis is to stop using the stimulant and begin a course of antipsychotic medication. Recovery from a drug-induced psychosis is not always immediate; it may take days or weeks to clear. In some cases, the psychosis may last for years and require continuing the antipsychotic medication. Autopsy results show that heavy amphetamine use can cause permanent brain damage (Eisch, et al., 1998).

Each therapist's own history and personal experiences with smoking and other forms of tobacco use, and the diseases they cause, will strongly influence his or her feelings about tobacco and its associated ills. There is no denying that tobacco use is a health hazard. Consumption of nicotine, like any other addictive drug or

unhealthy habit, deserves exploration in therapy. For clients who want to stop, cognitive and behavioral interventions have proven to be most effective for changing habits. The psychotherapist can discuss with the client whether, in addition to psychotherapy, a nicotine substitute or a medication like bupropion or naltrexone might be beneficial. If medication is desired, an evaluation and prescription by a physician is necessary. Studies demonstrate that using a nicotine patch, in conjunction with bupropion, while continuing in therapy, leads to significantly higher long-term rates of smoking cessation than the use of any of these without psychotherapy (Jorenby, et al., 1999).

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