Knowledge Workbook II
Addiction Medication Unit

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Knowledge Workbook II

OASAS Addiction Medicine Unit
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Introduction

The New York State Office of Alcoholism and Substance Abuse Services (OASAS) established the Addiction Medicine Unit to provide an organizational capacity within the agency to build a relationship with the provider community around integrating addiction medicines into behavioral treatment protocols and to work with physicians, their associations and our sister agencies around medical issues as they pertain to healthcare for patients with substance use disorders.

Through the journey of developing this new organizational capacity, we have found that teaching counselors about addiction medications and the neuroscience of addiction is the best tool for helping professionals understand the promise of these new medications, as well as their limitations.

Some providers struggle with a confused philosophical approach to addiction treatment and the use of medication. With advancements in the study of neuroscience and addictions, and the development of new addiction medicines, the ability of providers to address the addictive compulsions, including craving, withdrawal and obsessive thoughts is significantly increased. There is clear evidence that addiction medicines should be incorporated into mainstream addiction treatment. To do so, however, requires reliable information learned from clinical trials and the integration of these medical protocols with behavioral treatment. Most importantly, both treatment providers and patients need to learn that these are medications, not drugs that are being recommended and can improve treatment outcomes for some patients.

To help educate the counselors and physicians who work with persons with substance use disorders, the Addiction Medicine Unit has produced a series of educational tools. This is the second in our Knowledge Workbook series, Knowledge Workbook II, to be developed to advance the knowledge of Credentialed Alcoholism and Substance Abuse Counselor (CASAC)/Credentialed Prevention Professional (CPP)/Credentialed Prevention Specialists (CPS).
A. ADDICTION MEDICATIONS
Neurotransmitters and Receptors

Addiction has been described as a “brain” disease. To understand addiction, we need to understand the workings of the brain, its neurotransmitters and receptors. Neurotransmitters are chemicals made by our bodies. When they bind to a receptor site (a specialized area of a cell that is modified after binding with a transmitter), the site is activated and a chain of events follows.

GABA, Norepinephrine, Dopamine and Serotonin are all non-opioid neurotransmitters. The brain also manufactures opioid transmitters, called endogenous opioid peptides, which are grouped into three categories: Endorphins, Enkephalins, and Dynorphins. Many medications for addictions and psychiatric disorders work because of their effect on these neurotransmitters (by decreasing or increasing the amount of these chemicals at a receptor site) or through their effect on the receptor site (by blocking or stopping activation).

To further explain the relationship between neurotransmitters and addiction, let’s look at gamma aminobutyric acid (GABA), one of the major inhibiting neurotransmitters in the brain. GABA affects 20% of all receptor sites. When a sedative abuser, for example, uses a large amount of sedatives (an inhibitor) which mimics the GABA effect, the brain will decrease GABA production. But if the sedatives are abruptly withdrawn, with the production of GABA decreasing, neurotransmitters under GABA control will rebound. The patient will have norepinephrine excess that increases reflexes and blood pressure. Additionally, dopamine excess will cause hyperactivity, tremors, seizures, hallucinations and delusions. This loss of GABA’s inhibitory effect (no sedative use) leads to sedative withdrawal.

Serotonin modulates moods and affects appetite control, sleep initiation, temperature regulation and some cardiovascular function. Depression is thought to be due to a decrease in the production of serotonin or an ineffective function of the serotonin receptors. The serotonin reuptake inhibitor group of antidepressants (e.g. Prozac, Paxil) increases serotonin levels at the receptor level.

Dopamine is a neurotransmitter that works in the mesolimbic brain system and impacts mood and thought through the pleasure pathway. Cocaine causes an inhibition of dopamine reuptake; thus, more dopamine is available to the receptor, and a pleasurable, reinforcing event occurs with its use. A decrease in dopamine, for example, is involved in depression and Parkinson’s disease, while an increase in dopamine is thought to be involved in the etiology of Schizophrenia. Norepinephrine is a neurotransmitter in the same class as dopamine. It is a stimulant neurotransmitter that regulates mood and maintains sleep. A decrease can cause depression, while an increase can cause mania or anxiety.
Opiate transmitters activate different sites (Mu, Kappa, Delta, Lambda, and Epsilon) and can cause euphoria, analgesia, respiratory depression, small pupils and gastrointestinal changes. These effects are very similar to opiate drugs and medications.

To know addictions, one must know the brain; to know the brain, one needs to understand its neurotransmitters.
New Addiction Medications + Clinical Behavioral Treatment
“The New Frontier”

In a press release from Yale University on April 25, 2001, we learned that blood flow to the brain indicates when recovering cocaine addicts are able to benefit from talk therapy. Although the testing used to determine the cerebral perfusion, single photon emission computer tomography (SPECT) is not always available and may be expensive, this study shows that measuring blood flow to the brain may be a useful way to determine when a recovering cocaine addict is able to benefit from cognitive behavior therapy as a treatment for cocaine addiction.

Cocaine constricts coronary and cerebral blood vessels, but the consequences on brain function until now have been unclear. To determine the effects on brain function, Gottschalk and his colleagues measured the cerebral perfusion, or blood flow, of two women -- Ms. A and Ms. B -- twice over the course of their participation in a 28-day treatment program for cocaine addiction. The women also underwent neuropsychological testing to measure their ability to perform certain tasks. The study, supported by grants from the National Institute on Drug Abuse, measured cerebral perfusion.

Measuring the cerebral perfusion of cocaine addicts in treatment is critical because cognitive behavior therapy relies on changing behavior and affective responses by teaching coping skills and by addressing and modifying dysfunctional thought patterns. Most substance abuse programs include education about addiction, anger management, and motivational enhancement in both individual and group settings to provide alternative responses when an addict is faced with unmanageable feelings, urges or circumstances. “The capacity to respond to such ‘psychosocial’ intervention is largely dependent on a patient’s cognitive flexibility,” Gottschalk said. “We predicted the change from baseline perfusion would correlate with a measure of the capacity to learn new behavior. We found evidence to support this idea in the two cases presented.”

- **ONDANSETRON** is a medication used to treat nausea in chemotherapy patients and is sold under the name Zofran®. This medication appears to work through the serotonergic system. Serotonin is implicated in alcoholic drinking behavior, especially in regard to the serotonin3 receptor and its effect on dopamine. In alcoholics, it is possible that reduced serotonergic function results in a heightened sensitivity of the serotonin3 receptor. If this receptor could be blocked, there would be a decrease in alcohol-induced dopamine release, resulting in a decrease in alcoholic drinking behavior.

**Ondansetron Research Notes:** In his work with this serotonin antagonist, Dr. Bankole
Johnson found that 4 micrograms of ondansetron per kilogram (.25 mg twice a day) seems to have the maximum effect. He also showed that early onset alcoholics (early age, broad range of antisocial behaviors, and a high family prevalence) did well with ondansetron and naltrexone combined, though this was only studied in 20 patients.

- **NALMEFENE** is an opioid antagonist similar to naltrexone (ReVia). Recent research demonstrated that it may have advantages to naltrexone because there is no risk of liver toxicity, higher biologic activity than naltrexone (less is more), and it is longer acting.

  **Nalmefene Research Notes:** Dr. Barbara Mason's research showed that patients treated with nalmefene during a 12-week trial were 2.4 times less likely to relapse from alcohol than those treated with a placebo. Dr. Elie Nuwayser is working on an injectable, sustained-release form for nalmefene.

- **GABAPENTIN** is an anticonvulsant sold under the name Neurontin®. It is being used for pain management and anxiety, though some of the more interesting work is in the field of insomnia, a problem that is very common among alcohol-dependent patients.

  **Gabapentin Research Notes:** Dr. Kirk Brown is studying its use in alcohol-dependent patients and has had good results in ameliorating the insomnia, when increased as needed (up to 1500 mg per day).
Acamprosate

The Food and Drug Administration (FDA) granted a priority review to Forest Laboratories Inc.'s new drug application for Acamprosate (calcium acetylhomotaurine) for the treatment of alcoholism. Used to treat alcohol dependence in many European countries, this drug was on track for an expedited review. Forest officials have said that Acamprosate should not be used as a stand-alone addiction treatment, but in conjunction with counseling and other behavioral therapy. (ADAW, March, 2002) However, Acamprosate is still a long way from Federal Drug Administration approval for use in the United States. Although an advisory panel voted 8-2 to recommend the drug to the FDA as "effective" in May 2002, the FDA said that the data submitted did not adequately establish its safety and efficacy. The FDA has requested that at least one additional U.S clinical trial evaluating safety and efficacy be conducted as well as additional pharmacokinetic analyses and additional pre-clinical studies, according to a news release from Forest Laboratories, the company that will market the medication in the United States. (http://alcoholism.about.com/library/weekly/aa020916a.htm)

The high rate of relapse in alcohol - dependent patients has led to researching both old and new pharmacologic agents as treatment options for alcohol abuse. Researchers are studying withdrawal and aversion medications, as well as therapeutic medications for comorbidity and to reduce cravings to prevent relapse. In the last group, ReVia has been used for several years and, hopefully, Acamprosate will prove to be effective and become available in the United States. Commercially available in France since 1989, more than 1.3 million patients have been treated with this medication. Acamprosate, calcium acetylhomotaurinate, has a chemical structure similar to the neurotransmitter gamma - aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain. It is believed that Acamprosate stimulates GABA transmission which decreases the craving for alcohol. Acamprosate also has a binding site on glutamate receptors, an excitatory neurotransmitter, and inhibits its release. When alcohol consumption is stopped, there is a hyperexcitable state that is, at least partially, due to the glutamate system. It may take up to a year of abstinence for the neurons to readapt; Acamprosate may restore receptor tone in the glutamate system at a faster rate, but does not appear to cause an antidepressant effect.

Studies published by Volpicelli and colleagues using Naltrexone (ReVia) showed a relapse rate of 23% in a 12-week period in their study group. With Acamprosate, Whitworth and colleagues showed a relapse rate of 19% in a 12-week study period. Patients taking this medication stated that they "seem to lose interest in alcohol." European studies of over 4000 subjects had good results in 11 out of 12 studies; these studies all showed a drop-out rate of about half.
In clinical trials, Acamprosate was shown to consistently increase abstinence rates when used as part of a multidisciplinary approach that included psychosocial or behavioral therapies, the news release said. The studies also demonstrated that side effects for Acamprosate were generally mild, with the most frequently reported side effect being diarrhea. The FDA panel reviewed three European trials and one in the United States in which recovering alcoholics were given either acamprosate or a placebo. The drug kept more alcoholics from drinking in the three European trials, but it did not "meet the main effectiveness goals" in more recent U.S. study, FDA officials said.

In the European trials, 62 percent of those taking the drug remained abstinent for a year, while in the United States only 46 percent stayed sober for a year. In all trials, for those who did not quit drinking, the drug reduced the number of days they drank during the year.

The panel said results may have been worse in the United States because most U.S patients were addicted to multiple drugs and only a third went through detoxification before starting Acamprosate or a placebo. All of the European subjects went through detox before trying acamprosate and were "motivated to quit."

Acamprosate has been well tolerated in the studies, in which the major side effect appears to be intestinal cramps and diarrhea. Acamprosate does not appear to have abuse potential and is not a hypnotic or anxiolytic. In studies in our country, dosage was determined by the subject’s body weight. If the subject was over 130 pounds, two 333 mg tablets were given three times a day. If under 130 pounds, two tablets were given in the morning, with one tablet at midday and one at night. In Europe, however, dosing was 2000 mg per day divided into two doses daily. **Acamprosate is not metabolized by the liver and 90% is eliminated unchanged in the urine without adverse interactions with other drugs.**

In an interesting study at the Department of Psychiatry of the University of Lausanne in Switzerland, Acamprosate was used in combination with Antabuse. It was found that there was increased effectiveness without drug - drug adverse interactions. Because of its effectiveness in Europe, its low toxicity to the liver and the high rate of alcohol abuse in the United States, Acamprosate continues to be a promising addiction medication.
Facts about Buprenorphine

Buprenorphine is a partial opiate agonist (agonist and antagonist properties). Like most partial agonists, it has a safer profile than that of a full agonist. It exhibits a ceiling effect, which means that once a desired dosage level has been achieved, additional dosing does not produce additional effects, eliminating the possible opiate overdose effects of respiratory depression and/or death. By combining it with Naloxone, it is hoped that the Naloxone will prevent both diversion of the drug and intravenous injection. The withdrawal syndrome seen with buprenorphine is much milder than that of other opiates.

Buprenorphine has been approved by the FDA for use in the United States as an opiate detoxification and opiate maintenance agent. There will be two forms of the medication (available in 2 mg and 8 mg sublingual (under the tongue) tablets: Subutex® - buprenorphine alone and Suboxone®, which is Buprenorphine combined with Naloxone. This combination form prevents intravenous use of the tablet after crushing; the user would get a diminished opiate effect. Doses for opioid dependence will range from 2 mg. to 32 mg. with the average being approximately 16 mg. and can be used for detoxification or maintenance treatment.

The Drug Addiction Treatment Act of 2000 allows physicians to prescribe narcotic drugs in schedule III, IV, V or combinations of such drugs, for the treatment of opioid dependence. Qualified physicians in New York State are those who: 1) have a subspecialty certification in Addiction Psychiatry from the American Board of Medical Specialties; or 2) are certified in Addiction Medicine by the American Society of Addiction Medicine (ASAM) or by the American Osteopathic Academy of Addiction Medicine (AOAAM); or 3) have completed not less than 8 hours of approved training; or 4) have participated as an investigator in a clinical trial of buprenorphine; and 5) are authorized by the federal government.

Treatment options for those who are addicted to opiates have been successful, yet relatively limited. Methadone maintenance has been the most commonly utilized intervention, but access to the treatment has been geographically limited. Buprenorphine treatment in physician office-based settings will soon be available for physicians and treatment programs’ use.

The Addiction Medicine Unit of the Office of Alcoholism and Substance Abuse Services (OASAS) is working closely with the Department of Health’s (DOH) Bureau of Controlled Substance to insure that Buprenorphine will be used to treat opiate - dependent persons in the manner that the Federal government intended. OASAS and DOH will be sending information to physicians about treating patients in New York State for opiate dependence with this new medication, as well as information about accessing the OASAS -
certified treatment system to help the physician link to a nearby treatment network. OASAS and DOH are planning to jointly sponsor continuing education for physicians.

Methadone, a very effective and safe medication, has been the most commonly utilized treatment for opiate dependence. The approval of Buprenorphine by the FDA increases the options for physicians and methadone treatment programs for those who are addicted to opiates.

It is hoped that approval of Buprenorphine will increase access to opiate treatment, particularly for younger users and individuals who have used opiates for a shorter duration.
ReVia

What is it?
In 1994, the use of naltrexone was approved for treatment of alcoholism. Naltrexone (ReVia) is a narcotic antagonist that blocks the pleasurable effects of alcohol and reduces cravings. “Craving” is defined as a powerfully strong desire and perceived need for an experience. Neurochemical alterations caused by chronic exposure to addictive agents form the biological basis of drug/alcohol cravings.

Manufactured by DuPont, ReVia is naltrexone hydrochloride, an opioid antagonist which completely blocks subjective effects of intravenous opioids for 24 - 72 hours. The mechanism of action is unknown, though it is thought to reduce cravings. Tested in placebo-controlled trials, it has been shown to double abstention rates.

ReVia is a non-addictive and safe medication which uses pharmacologic means to improve the likelihood of successful treatment for alcohol dependence. Acknowledging that alcohol dependence is really a medical disease, with powerful physiological components, points to an objective use of a medication to aid in the treatment of this disease. While this medication may not be for every patient suffering from alcohol dependence, it may aid a treatment program in offering yet another means to complement ongoing support and treatment.

What types of patients cannot take ReVia?
Patients who meet the following criteria:

- Taking opioid medications (must be off all opioids for 7 - 10 days)
- In withdrawal from or dependent on opioids
- Have acute or severe liver or kidney disease
- Have a positive urine drug screen for opiates
- Fail a naloxone challenge test (see PDR
- Pregnant women or nursing mothers.

Note: Medication has not been studied in those younger than 18.
What are possible side effects when using ReVia?

- Nausea
- Difficulty sleeping
- Anxiety
- Abdominal cramps
- Joint and muscle pains
- Headaches

Who is a candidate for ReVia?

The best candidate for ReVia is a patient with an alcohol-dependence diagnosis, who wants to use this medication as part of a comprehensive treatment plan and understands that this medication does not take the place of treatment. The patient must be opioid-free and with no signs of significant liver or kidney disease.

What is the dose of ReVia?

ReVia comes in 50mg pills and can be given by several different schedules:

- 50mg once a day
- 100mg every other day
- 50mg every third day
Baclofen

Baclofen, known as Lioresal®, is a GABAB receptor agonist (GABA is the predominant inhibitory neurotransmitter in the brain) that alleviates multiple sclerosis’ signs and symptoms of muscle spasticity and is thought to inhibit transmission of reflexes at the spinal cord. Off-label uses of Baclofen include treatment of trigeminal neuralgia, tardive dyskinesia and intractable hiccups. Alcohol and opiate withdrawal often cause a highly excitable state. Having agonist properties similar to an inhibitory neurotransmitter, this medication may reverse some of the signs and symptoms in the alcohol and opiate withdrawal.

Research has found that Baclofen reduced the voluntary alcohol intake of rats, and decreased alcohol craving and alcohol withdrawal syndrome intensity in alcohol-dependent patients. American Journal of Medicine (2002) documented a small study using 10 mg as an initial dose, followed with 10 mg every 8 hours for 30 days in 5 patients. Work presented in Alcoholism Clinical and Experiential Research (2000) supported Baclofen as reducing alcohol intake due to its anti-craving properties.

Baclofen has been studied in comparison to Clonidine for treating opiate withdrawal. A study in the Journal of Clinical Pharmacological Therapy (2001) documented the treatment of 62 opiate-dependent patients with Baclofen or Clonidine for 14 days in a double-blind trial. Maximum doses of Baclofen were 40 mg per day and .8 mg of Clonidine per day (The Clonidine dose appeared to be a fairly low dose for opiate withdrawal treatment). There were no significant differences between the groups' treatment retention or side-effects, although the Clonidine group had more problems with hypotension.

There is also research showing Baclofen's ability to reduce the GABA modulation of cocaine self-administration. Baclofen is available in tablets with the initial dose of 5 mg three times a day to a maximum of 80 mg per day for treatment of muscle spasticity. Hallucinations and seizures have occurred on abrupt withdrawal of Baclofen. Side effects included: somnolence, dizziness, paresthesia, nausea, vomiting, headache and constipation. There is a report of a Baclofen overdose (300 mg with alcohol) which led to severe respiratory depression requiring airway and respiratory support.

REFERENCES


• GABA modulation of cocaine self-administration”. Annual Meeting of New York Academy of Science 2000;909:145-58

B. CLUB DRUGS
Club Drugs Overview

As the popularity of all-night dance parties at clubs and bars increases, so does the use of dangerous chemicals know as “club drugs.” Because unregulated suppliers manufacture these drugs, they can frequently become chemically contaminated, causing unpredictable reactions. Many are colorless, tasteless and odorless. A drink can be spiked with the drug and its effects can facilitate intoxication and sedation. The use of club drugs has been linked to sexual assaults.

The most common Club Drugs are: MDMA (Ecstasy), GHB (G, Liquid Ecstasy), GBL (Blue Nitro), Ketamine (Special K), Rohypnol (Rophies), LSD (Acid) and Methamphetamine (Speed, Ice, Crystal). All have similarities, as well as specific features; their use is never benign. To follow is a brief description of these drugs:

- **MDMA**, chemical methylenedioxymethamphetamine, was first developed as an appetite suppressant; it was found to have stimulant and hallucinogenic properties. When ingested, the pill or capsule can cause an increase in heart rate and blood pressure, confusion, depression, anxiety and paranoia. The immediate effects can last up to six hours; psychological effects can last for weeks. MDMA is very dangerous in high doses and can cause heart attacks, strokes, convulsions and permanent brain damage.

- **GHB**, gamma hydroxybutyrate, originally marketed for its ability to release a growth hormone to build muscles, comes in clear liquid, white powder or tablet. It can cause intoxication, euphoria and sedation, and depress the breathing rate. Its effects can be seen ten to twenty minutes after ingestion, and can last up to four hours. A related drug, GBL, which is marketed as an industrial solvent used to clean circuit boards and degrease engines, breaks down in the human body as GHB. At a low dose, there is mild euphoria; unconsciousness occurs at a higher dose. The effects of any dose are very unpredictable.

- **Ketamine**, developed as an animal anesthetic, originally gained popularity as a hallucinogen, not unlike PCP. Ketamine can cause impaired learning and memory, high blood pressure, delirium, depression and even fatal respiratory impairment.

- **Rohypnol** is a member of the benzodiazepine class of drugs, similar to Valium and Xanax. Rohypnol dissolves easily in carbonated drinks and can cause impairment, specifically the inability to remember events that occurred under the drug’s influence for up to 12 hours and is one of the first drugs reported as facilitating date rape.

- **Methamphetamine** is a stimulant, similar to cocaine, but with a longer period of effect on the user. Like cocaine, it can cause serious health problems such as heart and neurological damage. Agitation, violent and psychotic behaviors, and memory loss can be seen with abuse of this drug.
• LSD is one of the many hallucinogens that are taken to distort a person’s perception of their surroundings. Users can develop numbness, tremors, nausea, as well as elevated heart rates, body temperature and blood pressure. Two long-term complications, a persistent psychotic state and flashbacks, have been reported.

The club scene can be very provocative to adolescents and young adults, enabling an increased availability and use of these drugs.
Gamma Hydroxybutyrate (GHB)

The popularity of all-night dance parties at bars has increased. With these raves, the use of dangerous chemicals is on the rise. Although this FYI will specifically discuss GHB, it is important to remember the others noted in the previous FYI: MDMA (Ecstasy), GBL (Blue Nitro), Ketamine (Special K), Rohypnol (Rophies), Methamphetamine (Speed, Ice, Crystal) and LSD (Acid). Note: As of January 2000, the Drug Enforcement Administration documented over 5,700 overdoses and law enforcement encounters, as well as 65 GHB-related deaths.

Gamma hydroxybutyrate (GHB) is related to GABA, which is the main inhibitory neurotransmitter in the brain. GHB’s actions and withdrawal syndromes can be thought of as very similar to other inhibitors, such as sedatives and depressants. Developed in 1960 as an anesthetic, GHB has been studied outside the United States as a potential treatment for opiate withdrawal, alcohol dependence (Dr. Gian Luigi Gessa of the University of Cagliari in Italy), and narcolepsy. Since 1990, GHB has been abused in this country for its anabolic (body-building) effects and euphoria. It has become known as the “date rape” drug. GHB has not been sold over the counter since 1993, but can be purchased over the Internet. It is known as: Great Hormones at Bedtime, Salty Water, Gamma, Liquid E, Liquid X, Grievous Bodily Harm (GHB), Somatomax, Scoop, Georgia Home Boy and Organic Quaalude.

Other substances, appearing with increasing frequency, are similar in effect and chemical structure to GHB. One of these is Gamma butyrolactone (GBL), a chemical cousin of GHB and frequently marketed as an industrial solvent used in the polymer, pharmaceutical and agriculture industries to clean circuit boards and degrease engines. In the body, it converts to GHB. Another chemical compound, 1-4 butanediol, known as BD or 1-4-BD, is also related to GHB and GBL.

GHB comes in the form of a white powder that can be dissolved in beverages or a liquid in small bottles or vials. It is usually purchased in nightclubs combined with water in clear plastic water bottles. A dose is administered by taking a “swig” from a bottle for $5-$10. Effects occur within fifteen minutes and can last three to six hours. In low doses, GHB creates feelings of relaxation by slowing breathing and the heart rate and affects balance and motor coordination. In higher doses, deep sleep occurs. Users describe its effects as euphoric, restful and refreshing. Adverse overdose reactions include: vomiting, loss of consciousness, seizure-like activity, respiratory arrest, coma and death.

Tolerance and dependence can develop, causing withdrawal when use ceases. Withdrawal occurs in patients who have used GHB on a consistent dosing schedule for several months. Withdrawal symptoms appear within 1-6 hours after the last dose and include: anxiety, restlessness, insomnia, tremor, confusion, delirium, hallucinations, rapid heart rate, elevated blood pressure, nausea and vomiting. These can last
from several weeks to several months and the syndrome is very similar to patients withdrawing from sedatives, such as Benzodiazepine. Treatments for both are also similar, using anticonvulsants, depressants, anti hypertensive agents and anti-psychotic medications, as needed, to alleviate the withdrawal symptoms.

REFERENCES

- "Fact Sheet: Gamma Hydroxybutyrate (GHB)." Executive Office of the President, Office of National Drug Control Policy (November 1999)

What is “Special K?”

Special K is being widely used as a Club Drug. Deaths and overdoses have been reported. This drug is a serious concern, especially in light of its frequent use as a Club Drug by young adults.

“Special K”, or ketamine hydrochloride which is a cyclohexylamine anesthetic, sometimes referred to as a dissociative anesthetic. PCP, the famed elephant tranquilizer, is another example of this class of drugs. “Dissociative” refers to the feeling that these drug cause, a separation from the body or the environment.

Ketamine is also known on the street as K, Ket, Vitamin K, Keets, and Kit-Kats. Being under the influence of Ketamine is called being "in the hole," in K-Land," or "in the K-Hole." In June 2000, NYS OASAS Street Studies Unit reported in NIDA's Epidemiologic Trends in Drug Abuse that Ketamine is sold on the street for $20 a dose. In Miami, it is sold for $70 per vial. Ketamine is frequently obtained through veterinary hospital thefts, as reported in this NIDA publication.

Ketamine was first synthesized in 1962 in Parke-Davis' labs by the pharmacist, Calvin Stevens, to be used as an anesthetic. The first mention of recreational use of Ketamine is noted in 1965 and the term "dissociative anesthetic" was coined. Originally patented for use in humans and animals as an anesthetic and available by prescription as Ketalar, it was deemed illegal in the U.S. on August 12, 1999.

Ketamine is similar to PCP, but it is reported to cause a lower incidence of seizures and delirium because it is 10 - 50 times less potent. Ketamine can be smoked, snorted (frequently in place of cocaine), used intravenously or orally. Liquid Ketamine is used in veterinary surgery. Ketamine can also be mixed with other drugs of abuse to form, for example, "GK" (GHB and Ketamine) and "CK" (cocaine and Ketamine).

It is thought that Ketamine's action causes a decrease in the uptake of glutamate (an excitatory amino acid) by brain cells and acts as a noncompetitive antagonist of the MNDA receptor. Decreased uptake by the MNDA receptor decreases cell-to-cell communication. There is an acceleration of the natural process called “programmed cell death” (work done by Dr. John Olney at the Washington University School of Medicine). This work showed that cell life is preprogrammed; Ketamine speeds up cell death and causes them to die sooner. This is particularly important if used by pregnant women because of the effects on an unborn child. NIDA - supported studies have shown that prenatal exposure to Ketamine caused widespread damage to the developing rat brain – one of many reasons of concern about its use by humans). Other actions are thought to be promulgated through the opiate receptor, Mu.

Users of Ketamine are frequently seeking visual illusions, hallucinations, distortion of body image, feelings of strength and special insights (near-death-like experiences have been reported). Problems with
Ketamine use include: hallucinations, anxiety, feelings of doom, muscle rigidity, numbness, impaired motor skills, judgment and speech. In large doses, the user has been reported to have aggressive, violent behavior, blockade of pain sensation, seizures, ataxia, confusion, amnesia, and delirium with psychotic-like episodes.
C. STIMULANTS
Cocaine
An abused drug needing a treatment

How it works
Cocaine primarily affects the brain by blocking the reuptake pump for dopamine, serotonin and norepinephrine (neurotransmitters) in the presynaptic area of the neuron. This causes an increase of neurotransmitters in the synapse, enhancing their transmission. The areas of the brain that are most effected by cocaine include: the frontal cortex, nucleus accumbens and the ventral tegmental area. This area is known as the medial forebrain bundle and is involved in the euphoric effects of cocaine. Opioid molecules also appear to modulate the mesolimbic (reward) dopamine system.

Pharmacologic treatment approaches
There have been numerous attempts to treat cocaine dependence, withdrawal and craving with both pharmacological and behavioral treatments. The four main pharmacological treatments include:
- Substitution with a cross-tolerant stimulant, similar to the use of methadone to treat opioid addiction
- Treatment with an antagonist that blocks cocaine binding, similar to using naltrexone to treat alcoholism
- Treatment with a medication that antagonizes the effects of cocaine (reduction in reinforcement or craving)
- Alteration of drug metabolism to enhance elimination or cause a change in metabolite profile

What has been tried and what is new?
- N-Acetyl Cysteine, a medication used to treat cystic fibrosis, holds promise for reducing cocaine craving. It appears to restore glutamate to normal levels and also prevents glutamate spikes following cocaine IV drug use. (Peter Kalivas, Med. U. of South Carolina)
- Treatment with antidepressants shows mixed results.
- Treatment with Dopamine agonists (Anti Parkinson agents) - based on dopamine depletion. Bromocriptine and Amantadine have been used with mixed results and significant side-effects.
- Treatment with stimulants shows mixed results with some limited success and significant abuse potential.
- Anti-convulsant therapy - based on blocking kindling (increased neuronal sensitivity to a drug because of prior exposure) had mixed results.
- Amino Acid replacement: uses L-DOPA, a precursor of dopamine. Has no effect. Lithium treatment had no effect.
• Calcium Channel Blockers shows no efficacy.
• Combination of medications - bupropion and bromocriptine (antidepressant and dopamine agonist) have had questionable efficacy. The combination of Fenfluramine, a serotonin releaser and phentermine, a dopamine releaser has also had questionable efficacy but more importantly has had significant lung toxicity in some patients.
• Propranolol (Inderal®) has been used in research at the University of Pennsylvania in patients in the first weeks of recovery. Patients with severe cocaine withdrawal have been found to be very sensitive to adrenaline which can cause significant anxiety. Propranolol worked to block the anxiety - producing effects of adrenaline (Drug and Alcohol Dependence, April 2001)
• Methadone when used in high doses has been noted to decrease cocaine use in some patients, though Buprenorphine, (Tennant, et al., Journal of Addictive Disease 1995 14:67-74), the opiate partial agonist has been used with limited success.

Behavioral Treatment Approaches
Behavioral approaches that have been attempted to deal with this addiction have been very diverse, ranging from aversion therapy to community reinforcement with contingency management. Aversion therapy has used artificial cocaine substitutes, one being Articaine® (tetracaine, mannitol, quinine) which is paired with an emetic. This medication is snorted by the patient and nausea and vomiting occurs after use. The results have been mixed.

Several studies show that highly structured cognitive - behavioral treatment is particularly efficacious (Carroll, et al.) Some cocaine abusers have found self-help programs, which use fellowship and mutual support through regular group meetings, as a path toward recovery from addiction. Coping skills training is also being used as part of treatment programs to help cocaine abuse patients identify situations that trigger their urges to use cocaine and modify their behavior to avoid drug use.

On The Horizon
Research teams in the Netherlands and at NIDA have found that the cannabinoid system that governs the pharmacological actions of marijuana in the brain, also plays an important part in the neuronal cause of relapse. Thus the CB1 cannabinoid receptor is a promising new target for pharmacological intervention to prevent cocaine relapse and a study using the CB1 receptor antagonist, SR141716A, has reduced relapse and cocaine - seeking behavior in lab rats.
REFERENCES

Amphetamines and Methamphetamine

According to the National Household Survey on Drug Abuse, an estimated 14 million Americans used an illicit drug in 2000. The Survey found that an estimated 8.8 million people (4% of the population) have tried methamphetamine at some time in their lives. With the exception of cannabis, methamphetamine/amphetamines are the most widely abused illicit drugs worldwide. Methamphetamine abuse was more prevalent on the West Coast of the United States where English-speaking Caucasians were the predominant users. Now its use is becoming popular among Latinos, Asians and gay males in the East.

In the 1980’s, manufacturers produced D-methamphetamine, the most potent form of methamphetamine. D-methamphetamine has become the dominant methamphetamine illicitly manufactured in the United States. L – methamphetamine can be found in certain over-the-counter nasal inhalers. It should be noted that a person can test positive for amphetamines if using these nasal inhalers. The lab can be asked to specify which amphetamine was found in the urine.

Under the Federal Control Substance Act (1970), stimulants such as methamphetamine were categorized as a schedule II medication, which indicates that methamphetamine is acceptable for use as a medicine but has a high potential for abuse. A tolerance to the stimulant properties of methamphetamine can develop after a few weeks. To compensate, users engage in a spiral pattern of ever-increasing dosages which can result in a greater risk of overdose, coma and death.

There are medical diagnoses for which methamphetamine/amphetamine is used, such as narcolepsy (sleep disorder), attention-deficit disorder and short-term use for obesity.

Frequently used as a stimulant to lose weight and to reduce fatigue, methamphetamine was developed in the early 1900’s from amphetamine. It is a white, odorless, bitter-tasting crystalline powder. Amphetamine and methamphetamine act on the norepinephrine, dopamine and serotonin systems. MDMA, (methylenedioxymethamphetamine) and commonly known as Ecstasy, is also related to this drug group.

On the street, methamphetamine is known as Crystal, Tina, Christina, Crank, Ice, Speed, Glass, Meth or Chalk. It can be sniffed, swallowed, injected, smoked or dissolved in liquids such as water or alcohol. Methamphetamine pills can be taken orally or crushed and snorted. Tablets can be stirred with water and injected intravenously.
How it works
Amphetamine and methamphetamine cause the release of high levels of dopamine into the pleasure/reward center and block dopamine reuptake into the nerve terminal. This results in a higher level of dopamine being available to stimulate the nerve ending. There is a great potential for abuse because of the quick ‘high’ from its rapid onset. Snorting these drugs produces a high within 3 to 5 minutes. Oral ingestion produces a high within 15 to 30 minutes. However, neither snorting nor oral ingestion produces a rush as intense and brief as that associated with crack. Intravenous users and smokers of methamphetamine experience an initial rush that lasts from 5 to 30 minutes, compared to the 2 to 5 minute rush experienced from crack.

In its pure form, methamphetamine resembles crystals (looks like rock salt) and can be smoked. One form of methamphetamine that is smoked is called “Ice.” The use of Ice is largely restricted to Hawaii and the West Coast. Recently, several street contacts in New York reported that they smoked a form of methamphetamine called “glass.”

Smoking methamphetamine produces a high that is reported to last from 7 to 24 hours. The purity and rapid onset of the high makes it difficult for the smoker to monitor his or her use of this illicit drug, contributing to its potential for overdose. Methamphetamine is smoked in a special glass pipe. Although users have been known to inhale methamphetamine heated on aluminum foil, this practice has lost favor because users have begun to think that the use of the foil could contribute to Alzheimer Disease.

Short-term and long-term effects of methamphetamine
Initially, methamphetamine users are attracted to the sensations of invulnerability and elation they feel after using this drug. Initially, they may also experience increased energy, alertness, self-confidence, heightened endurance and sexual arousal. Physiologically, methamphetamine dilates the pupils, increases the heart rate, raises blood pressure, lowers appetite, and causes palpitations, dizziness, tremors, sweating, restlessness, headaches, diarrhea and dry mouth.

Long- term use can lead to severe psychological dependence and physical dependence. As one user noted, “Once you use it a few times, you continue to think about it long after you stop.” Other psychological effects include irritability, insomnia, hyperactivity, impaired social judgments, and auditory and perceptual hallucinations. Tolerance to the stimulant properties of methamphetamine develops after a few weeks. To compensate, users engage in a spiral pattern of increasing dosages that can result in a greater risk of overdose, coma and death.

It appears that methamphetamine users are slower to experience severe complications of addiction as compared to cocaine abusers. Prolong abusers become irritable and unstable. They may experience
impotence and changes in libido. They tend to show signs of social, emotional and intellectual
deterioration; some experience suicidal tendencies. In extreme cases, prolong use may lead to a
psychosis indistinguishable from schizophrenia.

Discontinuing the use of methamphetamine results in extreme fatigue, the “crash effect.” The person may
sleep for continuously for one or two days. This individual may also experience depression, paranoia,
heightened hostility and aggressiveness. Up to 50% of all dopamine - producing cells in the brain can be
damaged. The damage also appears to occur at serotonin - containing neurons, primarily at the nerve
endings or terminals, where they are reduced and re - growth is limited.

As with all drugs that can be injected, all the complications of IV drug injection are a risk (Hepatitis B,
Hepatitis C, HIV, etc.) Lead poisoning can occur as lead acetate can be used as a reagent in the
manufacturing process. Neonatal behavioral problems have been noted in the babies of pregnant
methamphetamine users.
Do You Know Where Your Ritalin Is?

Ritalin is a highly effective medication that has become another drug of abuse when used improperly. This abuse can cause very serious medical complications.

It is estimated that 2.5%-5% of elementary-school children have been diagnosed with Attention-Deficit Hyperactivity Disorder (ADHD). Stimulants often prescribed for this disorder are methylphenidate (Ritalin) and dextroamphetamine (Dexedrine).

Ritalin, the most commonly used medication to treat ADHD, is a schedule II drug manufactured by CIBA-Geigy in 5mg, 10mg, and 20 mg sustained-release tablets. Although similar to amphetamine, Ritalin is a milder central nervous system stimulant.

Thirty percent of the children with ADHD continue to demonstrate symptoms of the disorder at, or beyond, 18 years, the age of most freshman college students. Thus, while it is a highly effective medication when used correctly, the college setting becomes a place where others who have not been prescribed the medication can easily get access to it and there is little to prevent its abuse. This psychostimulant is being used as "legal cocaine" on college campuses, being used in larger amounts than prescribed for the ADHD patient or used by their non-ADHD friends simply as a stimulant.

Stimulant abuse is not new. Chinese physicians used Ma-Huang more than 5000 years ago. Its active ingredient was ephedrine, a stimulant. Amphetamines were synthesized in 1887 and were abused during the WWII era. In 1994, there were more than 150,000 emergency room visits involving cocaine, amphetamines and other stimulants. Ritalin, (often called Vitamin R, R-ball, the Smart Drug or Poor Man's Cocaine), is available to teenagers and college students for $1 to $15 per pill. It can be crushed and inhaled or smoked. Recently it has been mixed with heroin, rather than cocaine, to obtain a "speedball" effect. Intranasal use of Ritalin is responsible for at least one death, as reported in the Journal of Forensic Science.

Stimulants, particularly Ritalin, are abused for their euphoric effect. But it can also be used to increase alertness when studying for exams and as an anorectic to lose weight. Athletes have used Ritalin to improve endurance and minimize fatigue.

Toxic consequences of high-dose abuse or chronic use of this class of drugs includes: elevated blood pressure, elevated body temperature, seizures, psychotic ideation, violent behavior, high-risk behavior (sexual promiscuity, motor vehicle accidents), cardiac rhythm disturbances, strokes,
diseases related to IV use (Hepatitis C, HIV), and lung disease related to the injection of the inert materials that are components of the Ritalin tablet.
Caffeine: The Most Widely Consumed Drug

Recent studies and TV coverage have highlighted uses or possible abuses of caffeine. Although most Americans do not think about caffeine use and abuse, alcohol and drug treatment programs are very attuned to these issues because caffeine is too often used as a stimulant by our patients.

Caffeine is a bitter substance, rarely found in its pure form, that was first isolated from coffee in 1821. “Decaffeinating” entailed grinding or crushing toasted coffee beans and leaching out the caffeine with hot water. (The caffeine from decaffeinated coffee was then sold to soda manufacturers because some laws stated that to be called “cola,” soda must contain caffeine!)

Caffeine content is variable, though an average cup of coffee has 100mg of caffeine; a can of soda has 50mg. In the United States, an average adult consumes 210mg of caffeine daily as compared to the Finns who drink at least twice that amount. Canadian Indians and Eskimos consume approximately 400mg per day, even though they drink tea.

Caffeine, considered safe and not really a drug, does have some negative aspects because it is a stimulant. Caffeine has been mixed with, and sold under the name of, other drugs for a stronger stimulant effect. For the person who doesn’t want to use illegal drugs or pharmaceuticals, caffeine offers legal intoxication. Restlessness, nervousness, muscle twitches, fast heart rates, sweats and stomach or bowel disturbances may appear if too much caffeine is consumed.

Withdrawal can occur from as little as one cup of coffee per day over several months. Withdrawal occurs 12 – 24 hours after the last cup. The most common complaint is headache, noted in 50 – 75% of users. The caffeine withdrawal headache is now thought to be the real cause of post-operative headaches, rather than the anesthesia, as previously believed. Tremors, fatigue and a flu-like syndrome may appear. These symptoms can last for up to a week.

Pregnant women who drink greater than 8 cups of coffee per day can have serious adverse effects. Spontaneous abortion and stillbirth have been reported. In the 1970’s, caffeine was blamed for pancreatic cancer, but this has never been proven. Medical concerns include the increase in anxiety, depression and insomnia when caffeine is used. Caffeine is not considered a “gateway drug” (leading to more significant drug use), though it is related to heavier cigarette use.

Caffeine has frequently been touted for its ability to increase intellectual performance. This has only been proven when performance was impaired due to fatigue or boredom, again, utilizing the stimulant effect. Recently, in the Journal of the American Medical Association, an article was published indicating that
higher coffee and caffeine intake was associated with a significantly lower incidence of Parkinson Disease (Journal of the American Medical Association, May 24/31, 2000 Vol. 283, No. 20 pp. 2674-2679).

Debate is heating up about the purposeful use of caffeine in soft drinks, with some suspicion being pointed at the industry for using caffeine to addict the users in the same way as nicotine was used to increase the market of smokers. (Today Show Aug. 15, 2000)

REFERENCES

D. CO-OCCURRING DISORDERS
Hepatitis C
A Medical & Psychiatric Disorder

HEP C presents significant challenges for patients, physicians and counselors. To follow is an overview of the possible psychiatric effects of Hepatitis C infection in patients, as well as psychiatric side effects of medications often prescribed to patients for this disease.

Hepatitis C virus (HCV) infection is the most common cause of chronic liver disease in the United States. Approximately 4 million Americans are positive for the HCV antibody; 75% have had a positive HCV RNA test and are chronically infected. Of the chronically infected patients, 15% will develop cirrhosis. Five percent of those with cirrhosis may develop primary cancer of the liver (Hepatocellular Carcinoma).

Patients with alcohol and drug abuse present significant medical challenges. However, HCV patients present with a critical psychiatric component that must be recognized and addressed. An Italian study published in Gastroenterology in 1996 by Taruschio et al. showed that 36.7% of HCV patients had a psychiatric disorder. Patients with the HCV infection have been found to be more likely to have psychiatric disorders than other viral hepatitis patients. For psychiatric disorders associated with Hepatitis C, etiologies are categorized to understand this co-morbid relationship:

- HCV infection alone
- HCV treatment utilizing Interferon causing the disorder
- Liver transplantation, rejection and re-infection

As this breakdown shows, not only is the disease associated with psychiatric co-morbidity, but the treatments are also known to have significant neuropsychiatric adverse effects.

HCV and Depression

In various published studies, data show that up to 30% of HCV patients have a diagnosis of depression; 60% of these patients require treatment. The reason for the high rate of depression in HCV patients is unknown, though some believe that they may suffer from a reactive depression related to excessive fatigue or concerns about their long-term prognosis. Additional risk factors for depression relate to their concurrent substance abuse.

An article by Johnson et al. in the American Journal of Gastroenterology in 1998 compared depressive symptomatology of drug users with HCV who have not received interferon treatment to non-infected substance abusers. It was found that 57.2% of HCV-positive subjects who were using drugs had significant depressive symptoms. This is compared to 48.2% of non-infected substance abusers who
showed significant depression. The study concluded that depression associated with interferon treatment might at least, in part, be accounted for by a pre-existing depression, especially in the substance abuser. These studies led to the recommendation that screening for anxiety and depression should occur before starting HCV treatment protocols.

Interferon and Psychiatric Disorders

Interferon alfa - 2b, as used in HCV treatment protocols, has a mechanism of action that is not completely understood, but appears to work as an antiviral and immunomodulatory agent interfering with viral replication and enhancing the ability of the immune system to recognize and attack the virus.

There are many adverse effects seen with the use of interferon which have a medical and psychiatric overlay. It is also important to consider that the interferon therapy may amplify symptoms of an underlying depression. In addition, flu-like symptoms, gastrointestinal distress and alopecia can all have a profound effect on the psyche.

The described neuro psychiatric side effects occur in greater than 20% of the interferon treatment population and include:

- Depression
- Irritability
- Somnolence
- Insomnia
- Suicidal ideation

In the study by Renault, he described psychiatric side effects of interferon fell into three categories:

- Organic Personality Syndrome:
  - Irritability
  - short temper
- Organic Affective Syndrome:
  - extreme emotional lability
  - depression
  - tearfulness
- Delirium:
  - consciousness clouding
  - agitation
  - paranoia
  - suicidal potential
These symptoms can appear one to three months after starting interferon treatment and can improve in three to four days after decreasing interferon. The symptoms resolved when therapy was stopped. The organic syndromes were seen in patients with the highest doses of interferon; delirium occurred in patients with severe hepatitis who also had previous organic brain injury, organic brain dysfunction or previous alcohol or substance abuse.

Why Does One Develop Depression from Using Interferon?

The pattern of personality changes suggests that the dysfunction is in the frontal-subcortical area of the brain. There is also a possibility of interference with or changes in the neurotransmitters of the brain, especially serotonin. Research has shown that patients treated with interferon have altered serum levels of tryptophan, a precursor of serotonin. (In fact, the decrease in serotonin could lead to an interferon-induced dementia syndrome.)

There may also be an effect of interferon on the serotonin transporter. Clinically, the use of selective serotonin reuptake inhibitors (SSRI) such as Paxil®, have been shown to work on the serotonin transporter level and treat the depression induced by interferon.

Duration of treatment with interferon may also play a role in the development and intensity of the depression. Compliance with the medical regimen may be affected if the depression is not aggressively treated. Interferon-induced depression carries substantial risk of suicide with one reported case of suicide after the discontinuation of interferon. Further, interferon side-effects tend to look like opiate-withdrawal symptomatology and one has to investigate the possibility of relapse and the onset of depression seen in active drug use.

Treating Depression from the Use of Interferon

The seriousness and frequency of the depression indicates the need for constant monitoring and vigorous treatment. Investigation into the treatment of interferon-associated depression has involved the use of opioid - receptor antagonists, stimulants and antidepressants (especially the SSRI group as previously noted). One study, reported in the New England Journal of Medicine, pretreated the patients before the initiation of interferon therapy, using paroxetine two weeks before the onset of treatment. Two of 18 (11%) of the paroxetine group developed depression, compared to 9 of 20 (45%) in those who did not use paroxetine. (It should be noted, however, that this study was in melanoma patients and the results may not be applicable to Hepatitis C. Also, the doses of interferon were larger than those used in Hepatitis C treatment regimens.)

An approach for assessing and managing the patient with interferon-induced depression has been published by Zdilar et al. and suggested the following:
Inform the patient about the risk of interferon-induced depression
Educate the patient to recognize symptoms of depression
Explain treatment options
Arrange a psychiatric evaluation before treatment, if: current or previous history of depression
history of psychiatric hospitalization history of substance/alcohol abuse or dependence family
history of depression/suicide attempt
Treat depression before starting interferon
Start interferon after depression is in remission
Closely monitor while on interferon therapy
Actively treat alcohol and substance abuse
Watch for alcohol and substance abuse relapse
Regularly screen with the BDI, Zung or other depression tool
At each visit, ask about depression, suicidal ideations
If depression develops during treatment, treat depression aggressively
Interferon can be continued if depression is not severe
If depression does not respond to antidepressants, the interferon dose should be decreased

Note: It is noted that Ribavirin, another medication used in HEP C treatment, does not appear to aggravate the neuropsychiatric side effects of interferon.

Transplantation and Psychiatric Disorders
In 1995, almost half of the liver transplants were performed on patients infected with HCV. The potential for adverse mental health consequences in the face of a physical illness is well recognized and the psychiatric distress of a chronic illness is frequently associated with a compromised quality of life. Psychiatric evaluation is suggested in all transplant patients prior to transplant, especially to help them deal with emotional and behavioral disorders that may reduce the chance of successful outcomes, as well as issues of anti-rejection regimens and death.

In the work by Gayowski et al., the HCV patient undergoing transplantation showed more depression, mood disturbances and psychological stress than non-HCV transplant patients. This did not occur due to a greater severity of liver disease and, in fact, the HCV patients showed a greater level of fatigue, loss of appetite, weight loss, sleep problems and pain.

Complicating the transplantation picture is the problem of recurrence of HCV hepatitis after transplant, as shown in the work by Singh et al. He reported that 41% of HCV patients had a recurrence of HCV.
infection after transplantation; 12 months after transplant, these patients showed a significantly poorer quality of life with worse depression and a lower physical function than other transplant patients.

Medication Issues, Psychiatric Disorders and HCV
When treating patients with hepatitis, one must be aware of the possibility of altered hepatic function leading to an altered metabolism of medications, especially antidepressants. The changes in metabolism could lead to toxicity. In a patient with liver disease and compromised liver function, encephalopathy can develop due to an inability to handle dietary protein. The use of antidepressants of the tricyclic class can cause impairment in the thinking processes due to their anticholinergic effects, adding to the encephalopathic impairment. A clinical picture of delirium can ensue. The use of benzodiazepines can worsen the delirium.

Recommendation
It is critical for physicians and counselors to quickly recognize the pre-existing depression, or depression caused by Hepatitis C or the side effects of HCV pharmacologic therapy! They must be treated with supportive therapy, modification of doses of interferon and psychiatric medications. Failure to do so may result in limitation of therapy, noncompliance with therapy and serious personal, interpersonal and mental health consequences.
Pain and the Addicted Patient

The treatment of persons with chronic pain has recently received significant attention in the field of medicine. In the addiction field, there has been research on persons with a history of opiate dependence who are under-treated or untreated for their pain (Portenoy & Payne, 1997; Brietbart et al, 1996), but there has been little examination of the prevalence or impact that chronic pain has in the provision and outcome of addiction treatment. Some health providers attribute pain complaints and requests for pain medication to drug-seeking behavior, rather than to a pain disorder. Unaddressed pain can result in illicit drug use, use/abuse of non-prescribed pain medication and mistrust between the patient and the physician. This document offers an explanation of the significant addiction medicine issues when addressing an addicted person with chronic pain, and the findings and implications of a pain survey that was administered to OASAS Addiction Treatment Centers and methadone maintenance patients.

Treatment of Chronic Pain

Pain is the most frequent complaint for which persons seek help from health professionals. Pain is a unique and complex experience and is defined by the International Association for the Study of Pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage.” A person’s threshold and reaction to pain is influenced by his or her culture, previous experience and anticipation, as well as other emotional and thought processes. The experience of pain is always subjective and can never be proven or unproven.

Physicians frequently encounter three types of pain in their patients: acute pain usually due to trauma or illness; cancer-related pain; and chronic non-cancer pain. Chronic pain syndrome has many defining factors which include intractable pain for six months or more with marked changes in behavior and restriction in daily activities. Frequently, a chronic pain sufferer will have had many tests, treatments and even surgeries without achieving relief. Often, for the patient with chronic pain syndromes, the pain itself becomes the primary problem and focus of treatment.

Due to the complexity of pain treatment and the potential for great benefits, as well as risks, the World Health Organization developed a “Step” system for treating chronic pain. The treating doctor moves from lower to higher steps as more relief is needed. Step I involves the use of non-opiate medication and adjuvants. Step II uses weak opiates, non-opiate medication and adjuvants. Step III involves the addition of strong opiates to the Step II plan.
Introduced in Step I, non-opiate medications are tried, with varying success, to treat painful conditions. Recently, the most effective medications have been the antidepressants and anticonvulsants. Antidepressants are rarely abused and some are excellent for both pain and insomnia. It has been found that neuropathy (pain and tingling sensations) caused by diabetes and shingles may respond well to this group of medications. A new seizure medication, Neurontin®, has also been used with mixed success. A novel approach is the use of a topical preparation derived from the oil of red pepper (Capsaicin®) to relieve the pain of shingles and arthritis. The drawback of Capsaicin® is that it must be applied three to four times per day and it can take up to four weeks before pain relief is achieved.

Other non-opiate medications frequently used are in the NSAID group (non-steroidal anti-inflammatory drug). These medications, examples of which are Motrin® and Naprosyn®, are non-addictive and generally do not cause mood or behavior changes. They do have side effects, however, especially gastrointestinal (stomach upset, nausea, and possibly ulcer formation). The two newest medications in the non-opiate group are called Cox-II inhibitors (Celebrex® and Vioxx®), and patients report fewer gastrointestinal side effects.

Adjuvants, which are also introduced in Step I, include a large spectrum of non-medication treatment options. Physical adjuvant approaches to treatment include stretching, exercise, application of heat and cold, massage and electric stimulation (TENS). Acupuncture has recently been approved by the National Institute of Health for treatment of arthritis, low-back syndrome and carpal tunnel syndrome. Behavioral techniques include relaxation therapy and biofeedback.

Step II allows the physician to add a weak opiate to the pain regimen. Unfortunately, there is a stigma and extreme caution associated with prescribing opiates, so much so that many chronic pain syndrome patients will still experience some pain because of a reluctance of the physician to prescribe in the higher doses. Physical dependence can develop after 2 to 10 days of continuous use of these medications, although this does not mean that the patient is an addict. Weak opiates include codeine, oxycodone and hydrocodone, usually used in combination with aspirin or Tylenol®.

Step III involves the addition of strong opiates to the Step II plan which include, for example, dilaudid, morphine and methadone.

Pain Treatment and Concerns about Addiction
Many chronic pain sufferers worry about becoming addicted to their pain medication. Too often there is a blurring of the distinction between physical dependence on a prescribed and monitored pain medication and addiction. Physical dependence occurs when an individual is exposed to a medication that causes a cellular adaptation, or more simply stated, the brain undergoes changes, especially after continued exposure to the medication. Withdrawal symptoms often occur if the medication is suddenly stopped. The
individual does not lose control of his or her life. Addiction, on the other hand, involves experience of problems and dysfunctions in the other areas of the person’s life, and a loss of control over the use of the chemical. There is continued use of the medication despite problems caused by this use. There is associated denial and dishonesty. Addiction is a complex, progressive, biological, social and potentially fatal disease.

Two conditions which are common to addiction and physical dependence are tolerance and withdrawal. Tolerance is the ability to use greatly increased amounts of a substance with less and less intoxicating effects. Withdrawal is the predictable group of signs and symptoms that appear following the abrupt discontinuation of, or rapid decrease in, intake of a substance that has been used for a period of time. Withdrawal symptoms should be fully managed by the prescribing physician for the physically dependent patient who is eliminating a medication.

Treatment of pain has become sophisticated in the last several years, but the treatment of a patient with an addiction history who is also in need of pain relief continues to be a challenge. When chronic pain and untreated addiction coexist, the challenge escalates significantly. For the patient who is in recovery from his or her addiction, the goal is the same as treatment for the non-addicted patient: reduction of pain and restoration of function. While informed consent is important with all patients, this group of patients will need the added explanation of the types of medication which may be needed in the course of treatment, and the signs and symptoms to look for which may warn of ineffective dosing. Most addictionologists agree that no medication is contraindicated when its value can far outweigh the risks. The physician must collaborate with the patient in making the decision as to whether or not to use a particular class of medications. Secondly, the physician and patient should work from a written treatment plan or contract that spells out all reasonable goals and policies of treatment (amounts to be dispensed, refills, replacement of "lost medications" and frequency of office visits). When there is regular and effective communication, the treatment of chronic pain syndrome can be quite successful.

The survey summary to follow describes the prevalence of self-reported pain in alcohol and substance abuse treatment programs. The survey results demonstrate the need for significantly more research into this condition, as well as the need for increased education for the addiction treatment professionals and the medical professionals who are seeing persons who are either actively addicted or in recovery from their addiction and also experiencing chronic pain.

Survey Summary: Chronic Pain Among Persons with Chemical Dependence
(Adapted from a Concept Paper for a NIDA Grant by Dr. A. Rosenblum of NDRI with participation of the NYS OASAS Addiction Treatment Centers)
Chronic pain is prevalent in the general population and believed to exist more frequently among persons who are drug dependent. There is emerging evidence that a sizable proportion of persons with a history of drug dependence are under-treated for their pain complaints. Moreover, there is little known regarding pain management practices among healthcare providers in addiction treatment settings.

The prevalence of chronic pain in the general population as identified in published reports has varied greatly. A review of 15 epidemiological studies of chronic pain reported prevalence rates that varied from 2 percent to 40 percent and cautiously estimated prevalence at 10 percent (Verhaak et al, 1998). A World Health Organization study of 25,916 representative patients in primary care centers across 15 countries reported a 22 percent rate of chronic pain with wide variation across centers; pain prevalence in the United States center (Seattle, Washington) was 17 percent. Yearly economic costs are estimated at $100 billion due to lost wages, medical care and insurance (Aronoff, 1985; Am. Pain Society, 1997). Surprisingly, there is little data on the prevalence of chronic pain conditions among persons with primary substance use disorders. Although the treatment of chronic pain has advanced in recent years, there is little data on the type of treatments that chemically dependent patients receive for their chronic pain complaints.

One recently published study of 248 participants at three Methadone Maintenance Treatment Programs (MMTP) reported a 61.3 percent prevalence for chronic pain (Jamison et al, 2000). Compared to MMTP patients without pain, these patients disclosed significantly more physical health and psychiatric problems and reported more use of medications (prescribed and non-prescribed).

Reasons for the under-treatment of pain among addicted populations may be a consequence of institutional barriers, treatment practices among healthcare providers and the chemically dependent person's reluctance to seek medical care. More specifically, under-treatment of this population may be due to the lack of access to healthcare providers, reluctance of healthcare providers to prescribe opioids to persons with a history of chemical dependence (especially opiate dependence), and reluctance among persons in pain to seek treatment either because they feel they would be stigmatized, the treatment would be of little value, or that prescription of opioids might mean they would resume an active addiction. (OASAS, 1998; Jamison et al, 2000)

In regard to methadone maintenance treatment (MMT), there may be confusion over the pharmacology of methadone as an analgesic and a maintenance medication (Portenoy et al, 1997). Because of tolerance, methadone prescribed for opiate dependence does not function as an analgesic (Payte et al, 1994). Therefore, methadone patients with pain, while still receiving their methadone maintenance prescription, could benefit from additional narcotic medication to control pain.
In 2000, a pain survey of current or former substance users across 5 different settings was undertaken: 13 short-term inpatient New York State Addiction Treatment Centers (N=531); a Brooklyn (N=241) and a Manhattan (N=153) methadone maintenance treatment program (MMTP); a medical research program of HIV-positive former/current methadone patients (N=46); homeless drug users who were not in treatment (N=46); and a private substance abuse treatment program in a suburban setting (N=79). This study documents the prevalence of chronic pain in this alcohol and other drug dependent (AOD) population and their use of medication for pain.

Pain severity and pain interference were measured with the Brief Pain Inventory [BPI] (Cleeland & Ryan, 1994). “Chronic Pain” was defined as having pain for more than 6 months and a score of 5 or more on the BPI item "worst pain in the past week" or 5 or more on the BPI pain interference scale. The BPI pain severity scale consisted of three items: worst pain, average pain and least pain. They were rated on a 0 to 10 point scale from “No Pain” to “Pain as bad as you can imagine.” The BPI pain interference scale consisted of seven items representing functional activities such as Walking, Sleep, and Relationships on a 0 to 10 point scale ranging from “Pain does not interfere” to “pain completely interferes.” Respondents were asked to rate pain that had occurred in the past week. Psychiatric distress was measured with a six item validated version of the widely used SCL-90 (Rosen, 2000).

Results of the Survey and Implications for the Alcohol and Other Drug Dependent Patient

Physical pain complaints were highly prevalent in all groups (>75%). Except for the homeless sample, a significant minority within each study group had chronic pain (24% to 39%).

**Figure 1: Prevalance of Chronic Pain Across Six Populations**

- Suburban Program: 12%
- Out-of-Treatment “Street” Sample: 39%
- HIV patients: 35%
- NYPD-MMTP: 38%
- HHC-MMTP: 24%
- Rehab: 29%
- ALL: 29%

Note: “Rehab” in all of the Figures and Tables refers to Inpatient Alcohol and Other Drug Dependent (AOD) Rehabilitation
Additional analysis was performed on the two largest samples: the “Rehab” (Inpatient AOD Rehabilitation) patients (N=531) and patients from the Brooklyn (N=241) Methadone Maintenance Treatment Program (MMTP). The results are summarized below.

Factors Associated with Chronic Pain

Variables associated with chronic pain for both the Rehab and MMTP samples were chronic illness, psychiatric diagnosis, frequency of psychiatric symptoms, and pain as a reason for first using drugs. For Rehab patients, chronic pain was also associated with being Caucasian, using more drugs, and higher drug craving. Among MMTP patients, chronic pain was also associated with age, time in methadone treatment, and with a longer period of abstinence from their drug of abuse.

Differences were also found in the type of drug used. Among Rehab patients, chronic pain was associated with marijuana use and with pills. Among MMTP patients, chronic pain was associated with less marijuana use.

In the multivariate analysis, the variables that were significant for both treatment groups were chronic illness and frequency of psychiatric symptoms. Among Rehab patients, chronic pain was also associated with pain as a reason for first using drugs, being Caucasian, higher drug craving and polydrug use. Among MMTP patients, chronic pain was also associated with psychiatric diagnosis and time in methadone treatment. (Specific type of drugs was not included as a covariate in the multivariate analyses.)

Medical Services and Medications Used for Pain

Nearly three-quarters of all subjects had used a drug for pain in the past three months. Patients with chronic pain were significantly more likely to have used over-the-counter (OTC) medications and illicit medications for pain. There was no difference between the two pain groups in the percent of patients using pain medication prescribed by a physician.

In contrast to the Rehab patients, MMTP patients with chronic pain compared with MMTP without chronic pain were significantly more likely to have seen a physician, to have seen a physician for a pain complaint, and to have been prescribed pain medications by a physician. Chronic pain was associated with the use of OTC pain medications, but it was not associated with use of illicit drugs (or alcohol) as a treatment for pain.

Among respondents with chronic pain, 71 percent of the Rehab patients and 76 percent of MMTP patients reported that they were interested in medical treatment for chronic pain. The majority of patients with
chronic pain reported that they had received a diagnosis for their pain complaint: Rehab patients 56 percent (69/124); MMTP patients 59 percent (53/90).

Description of Pain Complaints among Subjects with Chronic Pain
Rehab patients: The most frequent pain among Rehab subjects were back pain, headache and neck pain (50 percent to 75 percent of respondents); and the mean number of pains in the past week was 4.67. On the BPI, 46 percent had moderate to severe pain interference, while nearly all (95 percent) reported moderate to severe pain intensity.

MMTP patients: The most frequent pains were headache, back, knee and foot pain (50 percent to 75 percent). The mean number of pains was 4.96. On the BPI, 70 percent had moderate to severe pain interference, while nearly all (98 percent) reported moderate to severe pain intensity.

Summary and Discussion
The results of this survey indicate that chronic pain is prevalent among persons in substance abuse treatment. These two groups of substance abusers, Rehab patients and MMTP patients had several factors in common, and several differences, associated with chronic pain. Consistent with the Jamison et al (2000) survey of methadone patients, Rehab and MMTP patients with chronic pain reported more chronic illness and psychiatric symptoms. This finding is consistent with reports from the general population that find that chronic pain is associated with psychiatric distress and illness. The two samples differed, however, in terms of drug use, time in treatment and ethnicity.

Data suggests that Rehab patients with chronic pain appeared to be using illicit drugs to self-medicate. Although a greater proportion of MMTP patients had chronic pain, this disorder did not seem to be associated with illicit drug use. However, similar to Rehab patients, MMTP patients were using OTC medications. Higher severity of pain among MMTP patients is consistent with experimental studies demonstrating that methadone patients are more sensitive to pain than the general population and other drug users (Compton et al).

Findings from this survey indicate that there is a significant need for extending and improving pain treatment for persons who are co morbid for pain and chemical dependence, with specific attention necessary to those who are in methadone maintenance treatment.
Insomnia and Substance Use Disorders

Addictive disorder research is beginning to define the relationships between detoxification, early recovery and sleep disorders. Although detoxification and early recovery have always been associated with sleep disorders, the association between them is now under closer examination. The research encompasses the association between sleep disorders, the use of alcohol and/or drugs of abuse for self-medication and patient relapse. A study, by Brower, K.J. et al., “Insomnia, Self-Medication, and Relapse to Alcoholism,” documents the relationship between sleep disorders, detoxification and patient relapse. Since research in this area is still very limited, this particular study raises the awareness of the medical profession and increases the likelihood of further study. This publication discusses basic sleep knowledge and substance-induced sleep disorders.

What is Sleep?

Sleep is defined as a normal and recurring state of changed consciousness or partial unconsciousness from which one can be readily aroused. It is an essential part of life that is as fundamental to our health and well being as air, food and water. On average, a person spends about one third of their lives asleep. Due to its necessity, the disruption of restful sleep can result in the diminished quality of life and health. It is speculated that sleep aids in restoration of the central nervous system, conservation of energy, thermo-regulation, discarding irrelevant memories and information processing. (Sleep Cycles, 07/18/01).

Normal sleep consists of 4-9 hours of a 24-hour day with two broad phases: rapid eye movement (REM) and non-rapid eye movement (non-REM).

Non-REM sleep is characterized by slow and uniform brain activity with frequent body movements. Blood pressure, heart rate and respiratory rate during this sleep phase are low and steady. (Pacific Sleep, 07/13/01) This sleep cycle can be broken down into four distinct phases based on the size and speed of the brain waves that are generated by the sleeper. The biggest and slowest brain waves, delta waves, are found in stages three and four of the sleep cycle. It is very difficult to awaken an individual from stage four because the deepest sleep of the night occurs in this stage.

REM sleep is characterized by irregular brain activity, and is almost indistinguishable from that of an active, waking brain. During REM sleep, only the heart, diaphragm, eye muscles and smooth muscles are spared from decreased movement. It is characterized by rapid eye movements, muscle twitches, fluctuations in blood pressure, as well as variations in heart rate. It is less restful than nonREM sleep and is usually associated with dreaming. The function of REM sleep and dreaming is still under investigation, although, it has been suggested that it plays a role in information processing and memory. (Sleep Cycles, 07/18/01).
Normal sleep is a continuous and dynamic process. It has a complex sleep architecture all of its own, which is accompanied by predictable patterns of brain-wave activity that occur throughout the night. Typically, the normal sleep pattern begins with 80-100 minutes of non-REM sleep followed by about 15-20 minutes of REM sleep. As this cycle repeats during the night, the REM sleep increases and nonREM sleep decreases. Four or five of these alternating cycles are experienced in a full night of sleep. (Ambien, 07/13/01).

The amount of sleep required varies by individual and depends on many factors. As one ages, both the distribution of sleep in a 24-hour period and total sleep requirements change. Infants require much more sleep than adults, sleeping about 18-20 hours; 50% is REM sleep. At age two, total sleep time decreases to 10-12 hours, including the nap period. About one-third of total sleep time is REM sleep. By age 10, total sleep time has decreased to 9 hours each day and 25% is REM sleep, stabilizing at 7-8 hours in adulthood with 20-25% REM sleep. Therefore, with age, sleep tends to become lighter and more fragmented. (Spangler, F.A., 1997)

The basic mechanisms of sleep cannot be localized to a single neurotransmitter system or anatomic area. However, it has been stated that the sleep-wake cycle involves the interaction of many different neurotransmitters or nerve-signaling chemicals. For example, serotonin is a chemical messenger that plays a prominent role in the regulation of certain aspects of REM sleep, as well as the onset of nonREM sleep. Norepinephrine is a chemical messenger that helps regulate REM sleep and facilitates arousal. The role and interactions of these neurotransmitters in the sleep-wake cycle is not known. However, when the function of these chemical messengers is disrupted, sleep disorders can result. (National Institute on Alcohol Abuse (NIAA)-Alcohol Alert, 1998)

**What is a Sleep Disorder?**

In our culture, sleep disorders are very common. On average, 40 million Americans suffer from chronic, long-term sleep disorders each year and an additional 20 million Americans experience occasional sleeping problems. (National Institute of Neurological Disorders, 07/13/01) Sleep disorders can arise from many causes: dysfunctional sleep mechanisms, abnormalities in physiological functions during sleep, abnormalities of the biological clock, and sleep disturbances that are induced by factors extrinsic to the sleep process. The DSM-IV divides sleep disorders into four broad categories: primary sleep disorders, sleep disorders from other mental disorders, those due to medical conditions and substance-induced sleep disorders. These four broad categories are referenced below, but only substance-induced sleep disorders are discussed in detail in this FYI In-Depth.
Primary Sleep Disorders

Primary sleep disorders are characterized as abnormalities in the quantity, quality, or timing of sleep. The five major types are: primary insomnia, primary hypersomnia, narcolepsy, breathing-related sleep disorders and circadian rhythm sleep disorders. Primary insomnia is a symptom rather than a disease and is a difficulty falling asleep or maintaining sleep. Primary insomnia results in daytime fatigue, and impaired reasoning, judgment and mood. It is classified according to the part of the sleep cycle most affected: sleep initiation, sleep maintenance (frequent awakenings), or early awakening (terminal insomnia). It is the most frequently reported sleep complaint and is diagnosed if the sleep problem causes difficulty in the person’s social, school, work or other significant area of life.

Primary hypersomnia is associated with excessive amounts of sleep and excessive daytime sleepiness. Usually a person with hypersomnia has difficulty getting out of bed even after sleeping more than eight hours. People with this disorder often report that no matter how much they sleep, they do not feel rested and their sleepiness causes problems in work and social settings. (Adams, D.B., 07/24/01). In narcolepsy, breathing-related and circadian rhythm sleep disorders, abnormal behavior disrupts the natural rhythm of sleep. Even though these events can be traumatic and dangerous, they do not necessarily cause a person to lose much sleep. Often, these events are not remembered the next morning and most people do not suffer day time effects from these actions. The most common parasomnias are nightmares, night terrors and sleepwalking. (HeliosHealth.com, 07/18/01)

Mental and Medical Sleep Disorders

There are many mental/medical disorders that disrupt sleep such as: depression, posttraumatic stress disorder and chronic pain. Depression is a serious mental illness that can interfere significantly with an individual’s ability to function. Difficulty falling/maintaining sleep or oversleeping are often associated with depression. Among patients with depression, about 85% report insomnia and 10 – 15% complain of hypersomnia. (Clinical Frontiers, 01/12/00) Also, sleep studies have shown that depression can be linked to a number of changes in normal sleep pattern, including prolonged sleep latency, reduced total sleep time, reduced sleep efficiency, reduced stages 3 and 4 sleep, reduced REM latency and increased REM density. (Clinical Frontiers, 01/12/00)

Post-traumatic stress disorder (PTSD) is an anxiety disorder that is triggered by memories of a traumatic event. The most frequently reported complaints among individuals diagnosed with PTSD are sleep disturbances and are noted by recurrent nightmares and sleep continuity disturbances (trouble initiating or maintaining sleep). PTSD has also been associated with increased REM activity and REM latency under extremely stressful situations.
Chronic pain in the form of rheumatoid and osteoarthritis, headaches, and fibromyalgia, for example, can also be associated with a variety of sleep disturbances. These sleep disturbances include initial insomnia, frequent awakenings, decreased sleep duration, daytime sleepiness or fatigue, and non-restorative sleep. Sleep disturbances of this magnitude are experienced by approximately fifty to seventy percent of pain patients. (Clinical Frontiers, 01/12/00)

**Substance-Induced Sleep Disorders**

Substance-induced sleep disorders involve the use of, or exposure to, medications, toxins, alcohol or other drugs. Intoxication and withdrawal can also result in substance-induced sleep disorders. Recently, substance-induced sleep disorders and their importance in terms of best treatment practices for those with addictions is becoming more well recognized.

It has been shown that alcohol interferes with normal sleep patterns by disrupting particular neurotransmitters in the brain which control or regulate sleep. When these neurotransmitters are disrupted, disturbances can result. Small amounts of alcohol can cause early sedation or sleepiness, and is often used as a sedative. However, the use of alcohol as an effective sedative can be extremely misleading because the side effects that can result are usually even more harmful and detrimental to the natural sleep cycle. For instance, due to the natural elimination of alcohol from the body, arousal and sleep fragmentation can occur and the second half of the sleep period can be drastically interrupted. This is due to the fact that, although alcohol will cause sedation, it will also decrease REM sleep in the first half of the night resulting in the rebound of REM sleep later in the night. When the rebounding of REM sleep occurs, it causes frequent awaking during the night, and suppression of REM sleep. Generally, with continued consumption, alcohol’s sedative effects decrease and its disruptive effects remain the same or increase. (NIAA-Alcohol Alert, 1998; Oscar-Berman, 1997; NIAA -NIH guide, 07/02/01)

Alcohol can be associated with sleep apnea. Sleep apnea is a disorder in which the upper air passage narrows or closes during sleep causing one to awake many times during the night gasping for air. Because of alcohol’s depressant effects, the muscles of the upper air passage are affected, snoring is increased and sleep quality and total sleep time are reduced.

Cocaine is a stimulant that produces a sense of euphoria and is followed in several hours by a sense of depression. The euphoria produced by cocaine occurs because of the effect that cocaine has on the brain chemical dopamine. Since dopamine is also involved in wakefulness, the use of cocaine can have an effect on sleep patterns. It typically reduces nonREM sleep and REM sleep. When cocaine use is discontinued sleepiness results causing one to use more cocaine to function. (Pacific Sleep, 07/13/01)

In a study by Weddington et al. (1990), cocaine withdrawal was examined over 28 days in male inpatients. In the discussion, the authors suggested that cocaine abstinence did not produce a "classic withdrawal
pattern” as seen with other drugs of abuse. However, with respect to sleep, the results showed that cocaine-dependent patients reported more difficulty falling asleep and significantly more wakefulness than those who didn’t use cocaine. Therefore, the cocaine withdrawal period can be initially associated with hypersomnia - excessive wakefulness.

Marijuana interferes with the normal sleep patterns. The active compound found in marijuana, delta-9-tetrahydrocannabinol or THC, interacts with specific chemicals in the brain that are associated with sleep and therefore, produces changes in brain wave patterns. The effects that can be contributed to this interaction depend on the amount of substance that is used. In small doses, REM sleep is only slightly suppressed, but large doses and/or continued use of marijuana can cause insomnia and significantly reduced REM sleep. (Pacific Sleep, 07/13/01)

Sleep Disturbances May Threaten Recovery

A variety of studies have been conducted which portray the relationship between alcohol and sleep. A number of these studies have indicated that alcohol’s subtle ability to sedate is reinforcing for some insomniacs and that the positive reinforcement could lead to dependence. For instance, studies have shown that 28 percent of those who complain of insomnia reported using alcohol to help them sleep. Individuals who reported having two or more weeks of insomnia were more likely to have met diagnostic criteria for alcoholism at one-year follow-up. (Ford, D.E. et al, 1989) Therefore, insomniacs should be made aware of the potential dangers of using alcohol as a sedative.

Alcohol withdrawal can also be associated with sleep disturbances. Studies have demonstrated that pronounced insomnia and marked sleep fragmentation often result when chronic drinkers go through withdrawal and that this may even occur many weeks into abstinence. Studies have also shown that non-REM sleep is reduced during withdrawal and ultimately restful sleep is diminished. Additionally, in some alcoholic, who attempt to withdraw from alcohol, long-suppressed REM sleep tends to rebound excessively, which can be associated with hallucinations. A symptom of alcohol withdrawal is delirium tremors (DT’s). DT’s is a condition that occurs 2-4 days after alcohol withdrawal, which consists of trembling and agitation with hallucinations, over-excitation, fever, sweating, and rapid heartbeat. Studied have suggested that these DT’s represent a state of continuous REM sleep. Given these findings, sleep disturbances may be associated with relapse during withdrawal and long-term abstinence. (NIAA-Alcohol Alert, 1998; Oscar-Berman, 1997; NIAA -NIH guide, 07/02/01)

In the study by Brower, K.J. et al., the frequency of insomnia and self-medication with alcohol for a group of alcoholics, as well as the relationship of these variables to alcohol relapse was investigated. The results revealed that patients with baseline insomnia were about twice as likely to report using alcohol to sleep as patients without baseline insomnia (55% vs. 28%). These findings suggest that insomnia may be a
predictor of relapse. This study was the first of its kind and many significant findings were found, there is little doubt that future studies will be conducted to make better treatment practices for those with addiction.

Treatment and Insomnia
It is evident that sleep is essential. Changes in sleep quality can be detrimental to health and well being. Screening tools that assess the pattern and quality of sleep are available and can be incorporated into treatment planning to treat patients with sleep disorders. One tool, for example, that is effective and widely used in evaluating sleep quality is The Pittsburgh Sleep Quality Index (PSQI). It can be easily administered in a traditional addiction treatment program. The PSQI was developed to: provide a reliable, valid, and standardized measure of sleep quality; to discriminate between “good” and “poor” sleepers; to provide an index that is easy for subjects to use and for clinicians and researchers to interpret; and to provide a brief, clinically useful assessment of a variety of sleep disturbances that might affect sleep quality. It differentiates “good” from “poor” sleepers by measuring seven different aspects of sleep: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month. The patient self-rates all seven of these areas based on a 0-3 scale. A total score of 5 or greater indicates a “poor sleeper.” This tool is useful to medical staff because it allows them to adequately assess sleep problems and determine what interventions, if any, are needed to treat the patient. It also provides the staff with the ability to follow up and assess the effectiveness of the intervention. (Buysse, D.J. et al, 1989)

When an individual is diagnosed with a sleep disorder, various treatment alternatives should be discussed with the patient. Many treatment options exist and include, for example: medication, acupuncture, yoga, tea/herbal remedies, biofeedback and meditation. Usually, the most effective treatment regimes are those that incorporate a combination of these therapies. Since each patient is different, effective treatment regimes vary depending on the patient needs. It has become common practice for a physician to treat substance-induced sleep disorders from a holistic approach, using relaxation and herbal therapies with less medication. Medications most often prescribed include: Vistaril®, Elavil®, Neurontin®, Trazedone®, Benedryl®, Ambien®, Sonata®, and Thorazine® with each of them having specific risks and benefits. In addition to these treatments, doctors often work with patients to help them restructure their daily living habits in such a way as to improve sleep quality as well. For instance, the doctor might instruct the patient to remove all stimulant use six hours prior to sleep, to go to bed and rise from bed about the same time each day, to avoid late meals and daytime naps.

Recommendations: Physicians and clinicians need to be aware of the growing body of evidence that exists about the relationship between substances of abuse and sleep disorders and they must recognize that when diagnosed and treated effectively, treating sleep disorders in those with addictions can improve their chances of recovery.
REFERENCES

- “Ambien: General Causes of Insomnia” http://www.ambien.com/professionals/about/normal.htm;
Prenatal Drug and Alcohol Exposure and Effects

While the harmful effects of ethanol on the fetus have been known since the writings of the Greek philosophers, Fetal Alcohol Syndrome (FAS) was first described by Lemoine in 1968 (France) and Jones in 1973 (U.S.). More recently, the effects of other drugs, legal and illegal, have also been studied.

The scope of the problem is significant as shown by the National Pregnancy and Health Survey of 1992 which showed that 5.5% of pregnant women used an illicit drug during their pregnancy. The breakdown of drug usage found in the study was:

- 2.9% Marijuana
- 1.1% Cocaine
- .5% Non-prescribed psychotherapeutic medications
- 18.8% Alcohol
- 20.4% Nicotine

The problems encountered with studying the effect of alcohol and drugs on the fetus include differentiation between the individual versus polydrug effect and the effect of the socioeconomic status on the fetus (poor maternal nutrition, poor prenatal care).

Of substances that are abused, alcohol has been the most frequently studied and appears to have the most severe, documented effects on the fetus, with 1 in 300-1000 births affected. Alcohol and possibly acetaldehyde, appear to have a direct toxic effect on the fetus and the placenta, where there is folate receptor activity impairment, as well as a decrease in the transport of amino acids and zinc.

FAS is the leading cause (85%) of mental retardation in children in the United States. The hallmarks of the Fetal Alcohol Syndrome are:

- Fetal growth retardation (involving weight, length, and head circumference being less than the 10th percentile for gestational age)
- Facial dysmorphism (classic abnormalities seen in the facial features)
- Central Nervous System dysfunction
- Other drugs have a less definite effect on the fetus, with prenatal growth retardation being the most common developmental abnormality seen.
- Opiates: low birth weight, prenatal depression (decrease in activity, respiration, glucose and calcium), increase incidence of SIDS, no clear teratogenic effect
- Cocaine: growth retardation, neonatal hypertension, irregular cardiac rhythm, increase in SIDS, teratogenic effect
- Marijuana: no significant teratogenic effect
- Nicotine: growth retardation, increase in SIDS, no evidence of teratogenicity
- Ecstasy: congenital defects seen (cardiac and musculoskeletal)

To help the mother and newborn, determining and treating a drug problem and prenatal exposure is critical. This starts with a good history and available prenatal and addiction care. Drug exposure urine testing has been used to determine prior use. More recently, meconium is being used to provide a better snapshot of the length of prior use.
Rapid Opioid Detoxification

Modern opiate withdrawal treatment dates back to 1975, where “electrosleep” (electroacupuncture) was developed in Asia, using high doses of naloxone intravenously. But this treatment produced several hours of severe withdrawal and was fatal for two patients.

In 1980, Kleber and Riordan developed a three-night in-patient protocol using clonidine and naloxone to detox patients addicted to heroin and methadone. From 1982 to 1986, Charney used a similar, but slightly longer, protocol fairly successfully. In 1988, Brewer published his work on the use of clonidine, naltrexone and valium, in a process called “deep sedation.” Described as a controlled state of depressed consciousness, it was also accompanied by partial or complete loss of protective reflexes, such as the gag reflex which could increase the likelihood of aspiration.

Newer and very highly controversial methods of detoxification incorporate the early components of general anesthesia and naloxone. Rapid opiate detoxification (RD) is a technique designed to abbreviate detoxification by precipitating withdrawal using an opioid antagonist, such as naloxone hydrochloride or naltrexone. Ultrarapid opiate detoxification (URD) represents a variation of RD in which the patient undergoes opioid antagonist precipitated withdrawal while under general anesthesia or heavy sedation. URD started in 1989 with the work of Presslich and Loimer in Vienna where they treated patients with barbiturate-induced anesthesia and intravenous naloxone. In 1995, LeGarda’s Cita Institute treated more than 3500 patients using general anesthesia.

Problems with URD initiated NIDA’s warning of unacceptable complications such as choking and cardiovascular consequences. Dr. David Simon in the Journal of Addictive Diseases in 1977 commented that the controversy around URD is founded in the safety of general anesthesia, paucity of URD controlled studies and the cost of the procedure.

New York State’s Department of Health and Office of Alcohol and Substance Abuse Services' DRG Clinical Panel on Drugs and Alcohol’s position statement on URD in October 1997 identified several problems with URD such as: anesthesia increases risks of morbidity/mortality; remaining in treatment post withdrawal is the key issue in treating heroin addiction, not withdrawal; inadequate evidence of URD’s long-term benefit and a lack of documented long-term benefit; and an inadequate demonstration of an appropriate risk/benefit ratio and that substantial initial costs may lead to a lack of funds for critical ongoing treatment. The Panel concluded that “the approach could have merit if research showed that long-term, patients were more likely to have remained opiate-free ... The Panel views the clinical application of UROD as experimental until such time as peer-reviewed evaluation of this technique is conclusive as to its benefits.”
Further controversy surrounding opiate detoxification has centered on the physicians performing implantable naltrexone in the abdomens of patients and the risks of post-operative complications and deaths (7 reported to date).
Elderly Alcohol and Substance Abuse

Alcohol and substance abuse among the elderly is a hidden national epidemic. It is believed that about 10% of this country's population abuses alcohol, but surveys revealed that as many as 17% of the over-65 adults have an alcohol-abuse problem. In his work at the University of Kentucky, Dr. Hays found that 2.5 million older adults and 21% of older hospital patients had alcohol-related problems. (Hays, L. et al. Presented at a symposium for the American Academy of Addiction Psychiatry 2002 Symposium: Substance Use Disorders in the Elderly: Prevalence, Special Considerations and Treatment.)

Elderly alcohol abusers can be divided into two general types: the "hardy survivors," those who have been abusing alcohol for many years and have reached 65, and the "late onset" group, those who begin abusing alcohol later in life. The latter group's alcohol abuse is often triggered by changes in life such as: retirement, death or separation from a family member, a friend or a pet, health concerns, reduced income, impairment of sleep and/or familial conflict. Because alcohol has a higher absorption rate in the elderly, much like it does in women, the same amount of alcohol produces higher blood alcohol levels, causing a greater degree of intoxication than the same amount of alcohol would cause in younger male drinkers. Alcohol abuse in this generation is complicated by the use of prescription and over-the-counter (OTC) medications. The elderly spend over $500 million yearly on medications. Combining medications and alcohol frequently result in significant adverse reactions. Due to a reduction in blood flow to the liver and kidneys in the elderly, there can be a 50% decrease in the rate of metabolism of some medications, especially benzodiazepines. Additionally, chlordiazepoxide (Librium®) and diazepam (Valium®) have such long half lives (often several days) in the elderly that prolonged sedation from these drugs, combined with the sedative effects of alcohol, can increase the risk of falls and fractures. The benzodiazepine user may become confused and take extra doses or other medications, causing overdose or death.

Serious consequences can result solely from OTC medication use, as well as combining them with alcohol. Laxatives, for example, can cause chronic diarrhea, which can lead to sodium and potassium imbalance and cause heart rhythm irregularities. Antihistamines, another popular OTC medication, can cause confusion; cold medications can elevate the blood pressure and lead to strokes. Caffeine is frequently added to OTC medications and can cause anxiety and insomnia. Often, mixing alcohol and the OTC medications increases the occurrence of side effects and can intensify negative consequences. Nicotine dependence is also a significant problem in the elderly, due both to their addiction and boredom. Use early in life sets the stage for morbidity and mortality from this addiction. Over 400,000 people in the U.S. die each year from smoking-related diseases. Elderly smokers not only continue to impair their respiratory systems, but are also more apt to die from respiratory diseases. Nicotine replacement products work successfully in this group, especially when combined with behavioral, supportive and other therapies.
What to look for?

The problem of elderly substance abuse may be difficult to detect when the elderly live alone. Friends and family may be reluctant to even consider that there may be a problem and medical evaluations often do not reveal substance abuse. Consideration should be given to the presence of a drug and/or alcohol problem if there is memory loss, depression, repetitive falls and injuries, legal problems, chronic diarrhea, labile moods, malnutrition and recent isolation. Elderly women are more likely to have a diagnosed or undiagnosed depression. According to Dr. Hays, prescription drugs, particularly benzodiazepines, may be abused by these women.

The Center for Substance Abuse Treatment published a list of signals that may indicate an alcohol or medication-related problem in the elderly:

- Memory trouble after having a drink or taking a medication
- Loss of coordination (walking unsteadily, frequent falls)
- Changes in sleeping habits
- Unexplained bruises
- Being unsure of yourself
- Irritability, sadness, depression
- Unexplained chronic pain
- Changes in eating habits
- Wanting to stay alone much of the time
- Failing to bathe or keep clean
- Having trouble concentrating
- Difficulty staying in touch with family or friends
- Lack of interest in usual activities

What to do?

- Education for and from healthcare providers, family and pharmacies is paramount. The healthcare provider can use simple screening tests such as the AUDIT-C, CAGE and/or the Short Michigan Alcoholism Screening Test - Geriatric Version (S-MAST-G).
- A family’s attention to the elderly family member’s daily life can be extremely helpful in identifying medical and social problems. It is important to develop a medication inventory for an elderly person. This inventory is a list of all of his or her prescribed and OTC medications. The final inventory usually uncovers a surprising number of OTC medications (some studies have shown as many as nine different medications used per month). This list of medications can be brought to a local pharmacist where a drug - drug interaction list can be generated.
• Another worthwhile consideration would be to try to increase the activity level and social interactions of the elderly family member. Senior groups and volunteer work are examples of ways to increase companionship and self esteem.

• Clinical treatment may need to be considered, as well as pharmacological interventions as a possible adjunct to clinical treatment. Naltrexone (ReVia ®) appears to work as well in the elderly as in other groups of alcohol -dependent patients to decrease the craving and feeling of elation related to alcohol use. Antabuse should probably be avoided because the elderly cardiovascular system may not be able to handle possible cardiac events that could occur with an alcohol-antabuse reaction.

• Twelve-Step, self-help and support group participation should be considered.

Project 2015
Pointing to the rapid growth in the elderly population in New York State, Governor George Pataki launched PROJECT 2015, requiring State agencies to work together to prepare for the impact of this growing population on New York State’s services. Alcoholism and substance abuse among elderly adults have been identified as priority issues affecting government policy, systems management and program operations.

As a member of PROJECT 2015, the New York State Office of Alcoholism and Substance Abuse Services submitted a brief on the nature and scope of alcohol and substance abuse among seniors. OASAS is working internally and with its constituency groups of providers, local government partners and consumer representatives to identify opportunities to integrate program development efforts with the Statewide PROJECT 2015.
E. OTHER DRUGS
Oxycontin "OXY"

Oxycontin is the tradename for Oxycodone HCL controlled-release tablets. It is manufactured by Purdue Pharma and is a pure mu-opioid agonist. Oxycontin is a schedule II controlled substance and is manufactured in 10mg, 20mg, 40mg, and 80mg tablets. Physicians prescribe this analgesic medication to patients with severe or chronic pain conditions because it is very useful secondary to its time-release feature. The strength is approximately 50% of a morphine dose.

On the streets, people are saying that OXY can produce a high so close to heroin that the black market sales are soaring. OXY is being sold on the street for $1 per mg, making a bottle of 100, 40mg tablets worth $4000. Opiate users crush the small white tablets to remove the time-release coating, then snort or inject the powder. The rush is similar to heroin. As a mu-agonist, the same risks are present as with heroin use, i.e. too large a dose can cause respiratory depression and death. Of course, physical dependence with significant withdrawal occurs with OXY use.

Although OASAS' Office of Applied Studies noted that their data from 1991-98 has not yet reported oxycontin as a drug of abuse in New York State, we are concerned that its widespread use in New England may soon spread to our state.

The medical community is being told to be more aggressive with the treatment of pain. However, this leaves the door open to illegal use, diversion and prescription forgery due to the very attractive street value. Many of the illegal sales have involved Medicaid-paid prescriptions, so many in fact that the Assistant U.S. Attorney, Helen Kazanjian, stated that she feels OXY use is "federally funded drug abuse."
Jimson Weed (Datura Stramonium)

Increasing numbers of youth in New York State are using this plant as a hallucinogen. Adolescents experimenting with the herb are generally unaware of its dangers. The public usually learns of Jimson Weed when users are hospitalized in critical condition. But its use is more widespread than recognized. Poisoning cases have been reported from a number of states, particularly in the west where the plant is more pervasive. Such incidences usually peak in the summer and early fall when the plant matures. The American Association of Poison Control Centers reported 152 cases of Jimson Weed poisoning nationally in 1998. A survey of the six New York State Poison Control Centers found an estimated 11 cases of Jimson Weed exposure in New York in 1998, accounting for over 7% of the national total, which may be an undercount since this only includes those reported to regional poison control centers. It should also be noted that young children are at particular risk when this plant is used as a houseplant or in ornamental gardens, and not recognized as dangerous.

It is legal to grow or sell this plant in New York State or in the US. Seeds can be bought through some seed companies and live plants are sold in some stores. Therefore, caution and education are the most important weapons to protect our youth from this toxic plant’s effects.

Datura stramonium is a member of the Belladonna alkaloid family and is a large annual herb that grows 3-5 feet tall. It grows wild in most parts of the US and southern Canada and has been called Green Dragon, Locoweed, Devil’s Trumpet, Devil’s Apple, Devil's Weed, Mad Apple, Thorn Apple and Stinkweed.

Its leaves are large (up to 8 inches long), jagged (4 - 15 points) and bitter-tasting; its flowers are white or purple, trumpet-shaped, and 2-8 inches wide. In the fall, the plant bears fruit that are green and spiny in appearance; the seeds are brown to black. The seeds and leaves are the most toxic parts of the plant, although all of the plant is toxic, including the flower and its nectar. Datura contains the toxic alkaloids called atropine, scopolamine and hyoscyamine and .7% of the fresh weight of the plant is made up of these alkaloids. The plant can be eaten raw, prepared as tea or smoked. Preparations of Datura are sold in health food stores as a treatment for asthma.

The toxic effects from use of Datura cause anticholinergic intoxication: dilated pupils, elevated body temperature, dry mucus membranes, urinary retention, decreased gastrointestinal motility, agitation, delirium, seizures, visual hallucinations, amnesia, spasmodic movement and coma. Symptoms usually appear 1-4 hours after ingestion and may persist for days.
Over-The-Counter Danger: DXM

Many have noted that over-the-counter (OTC) preparations are increasing in popularity with teenagers, possibly due to a belief that they are safe and because they are easy to procure and many Internet sites report on their ability to induce a "high." Abuse of cough medications is not a new phenomenon. Information about this abuse dates back to the 1950's when cough preparations contained codeine or similar compounds. In 1990, the FDA's Drug Advisory Committee held a hearing concerning the abuse of cough syrups with dextromethorphan (DXM).

DXM is a synthetically produced substance, the methylated dextrorotary analogue of levorphanol, a substance related to codeine. The cough suppressant ability of the opiates act on the cough center located in the medulla oblongata and raises the threshold of the cough reflex. It does not have other opiate effects such as analgesia, sedation, or constipation. DXM is found in over 75 OTC medications.

Recent research is examining DXM as an anti-epileptic, neuroprotector and anti-Parkinson agent. However, DXM's antagonism of the N-methyl-D-aspartate receptor (NMDA) by way of its immediate metabolite dextrorphan leads to its potential as a substance of abuse when used in greater than recommended dosages. Dextrorphan's effect can last 3 - 6 hours and cause a PCP intoxication - like syndrome. Thus, DXM has been classified as an dissociative agent, much like PCP and Ketamine. With DXM intoxication, one can see hyperexcitability, lethargy, ataxia, slurred speech, hypertension, elevated heart rate, nystagmus and hallucinations. It is also thought that DXM can cause the release of serotonin. If used with an antidepressant of the SSRI class (Prozac, Paxil, etc.), it can cause a potentially fatal condition know as the Serotonin Excess Syndrome.

Information from Internet sites advise and instruct the potential user on how to "trip" using DXM (called "roboing" or "robo-copping," a slang term derived from Robitussin) which is contained in Robitussin Maximum Strength, Vicks 44 and Drixoral Cough. The Internet sites also provide access for the purchase of purified pharmaceutical - grade powdered DXM through the mail. Instruction is given in mixing the powder with juice to avoid its bitter taste or how to obtain gelatin capsules that can be filled with the powder.

One site teaches the uninitiated how to dose DXM - called plateaus, being aware that a 4 ounce bottle of DXM cough syrup contains 354 mg DXM. The first plateau, 100-250 mg of DXM consumed, leads to euphoria. Plateau 2 is 250 - 450 mg and the user sees increased euphoria, and a decrease in the sense of time and surroundings. The 3rd plateau is 450 - 800 mg and includes plateau 1 and 2 reactions plus visual hallucinations. Even the Internet sites caution the user of the 4th (800-1800mg) and the 5th (over 1800mg) plateaus as being very dangerous with profuse sweats, extreme nausea and blackouts. Other problems with DXM use is that many of the OTC preparations are not pure DXM and may contain acetaminophen,
antihistamines or stimulants that can cause a severe side effect if taken in excess. Also, DXM can be found in the form of a bromide salt which can lead to bromide poisoning if large quantities are taken. Bromide poisoning is manifested by: behavior changes, headaches, apathy, irritation, slurred speech, psychosis, tremors, ataxia, hallucinations, weight loss, acne like rash, and coma.