New York State
Office of Alcoholism & Substance Abuse Services
Addiction Services for Prevention, Treatment, Recovery

ADDICTION FYI’S YEARBOOK
2010/2011
This yearbook is a compilation of all the Addiction Medicine Briefs and FYI’s sent out during the later part of the year 2010 and all of year 2011.

There will be at least one question asked per FYI and free CASAC credit can be earned by answering 75 percent or more of the questions correctly.

This yearbook contains the following FYI’s:

1. Old Medications with New Uses for the Addiction Toolbox
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Old Medications with New Uses for the Addiction Toolbox

Zonisamide is an anticonvulsant medication with GABAergic (inhibitory) and glutamatergic (excitatory) effects. Anticonvulsant drugs have been used in patients with alcohol dependence for several years to treat withdrawal and decrease craving and alcohol consumption.

In 2010, Arias et al. (J Clin Psychopharmacol. 2010; 30(3):318-22) reported that there was a significant medication effect favoring the zonisamide group for heavy drinking days, drinks per week and alcohol urge scores. However, there was not a significant effect on the number or rate of increase in abstinent days. Rubio et al reported similar data (Clin Neuropharmacol. 2010 Sep-Oct;33(5):250-3.) in that there was significant improvement observed in a visual analog scale for craving, weekly drink consumption, and γ-glutamyltransferase (one of the liver function tests).

Rubio and colleagues also reported (Pharmacopsychiatry. 2010 Oct 6. - Epub ahead of print) information on the use of Zonisamide for alcohol withdrawal treatment and compared it to diazepam. During the inpatient period both drugs reduced alcohol withdrawal symptoms, but the decrease was more marked in the zonisamide group. At the end of the study (week 3), participants treated with zonisamide showed lower CIWA-Ar (Clinical Institute Withdrawal Assessment for Alcohol, revised scale) scores than subjects receiving diazepam. Also, individuals in the zonisamide group had less craving for alcohol, less anxiety, and less daytime sedation compared with participants treated with diazepam.

The medication should not be used if the following conditions/diseases are present: liver disease, decreased sweating, fever, aplastic anemia (a blood disorder in which the body's bone marrow doesn't make enough new blood cells), kidney stone, metabolic acidosis (a clinical disturbance characterized by an increase in plasma acidity), renal disease, agranulocytosis (an acute disease marked by high fever and a sharp drop in circulating white blood cells) and suicidal ideation.

Disulfiram (Antabuse) is one of the current treatments for alcohol dependence that produces an aversive reaction when someone uses/drinks alcohol, thereby hopefully preventing administration. Disulfiram has also previously been shown to have an effect on cocaine addiction independent of its interaction with alcohol. Jason Schroeder from Emory University School of Medicine and his team (Schroeder etal. Neuropsychopharmacology 2010 Epub ahead of print) have looked at rat models of addiction. Disulfiram did not alter behavior for self-administration of food or cocaine, however, after an extinction of cocaine availability, disulfiram blocked the restarting of cocaine after drug-priming. This is evidence that while disulfiram does not alter the experience of taking the drug, it does potentially block relapses once a user has withdrawn from drug-taking behavior. The authors hypothesized that this was due to a reduction in noradrenalin (NA) in the brain due to disulfiram’s inhibition of its synthesizing enzyme, dopamine β-hydroxylase. NA, one of the neurotransmitters
thought to trigger relapse, was shown to be reduced in the brain in relation to the effective dose.

Despite the promise of disulfiram in the treatment of addiction, side effects include inhibition of other enzymes and damage of the liver. The research team wanted to find a medication that was similar in effect to disulfiram on NA levels but without the unwanted consequences.

**Nepicastat** is a medication that was used unsuccessfully for the treatment of heart failure. It is a dopamine β-hydroxylase inhibitor. Nepicastat administration caused both the reduction of NA and the behavioral effects on cocaine-primed behavior without the other harmful effects of disulfiram.

Researchers at the University of Texas Medical Branch at Galveston have recently completed a Phase I safety trial studying nepicastat for the treatment of cocaine dependence in human subjects and hope that the use of this medication will succeed in treating cocaine dependence safely.
Deadly Fentanyl

Fentanyl is a synthetic opiate that was introduced into medical practice as an intravenous anesthetic under the trade name of Sublimaze in the 1960s. Its use has been steadily increasing over the years. Fentanyl is much more potent than heroin and results in frequent overdoses that can lead to respiratory depression and death. Prescriptions for fentanyl more than doubled from about 2.59 million in 2000 to 7.64 million in 2008.

Drug-related fatalities are now at the top of the accidental-death list in a growing number of states, according to a report from the U.S. Centers for Disease Control and Prevention (CDC).

The U.S. Department of Justice says the availability of fentanyl is due not only to the increase of legal prescriptions but also because of its availability in other forms. U.S. medics in Afghanistan pack fentanyl lollipops in their kits to administer to critically wounded soldiers in the field because of its rapid and sure effects. Yet other military applications have been deadly. In 2002, the Russian government rushed a theater where 50 armed Chechens were holding almost 800 people hostage in a protest. At least 119 people died from the fentanyl-based gas the army dispersed to defeat the terrorists.

A good deal of the drug is stolen from pharmacies, nursing homes and manufacturers. There is also illegal manufacturing of fentanyl and reports of the drug being imported from Mexico.

There are other illegal methods. In January of 2009, Spokane police arrested a 19-year-old nursing home worker and her boyfriend for allegedly entering patient rooms and taking the pain patches off of patients.

According to the CDC and other sources, fentanyl is abused by the removal of gel from the patches. It is often “cooked” in foil and inhaled or injected. Patches are sometimes frozen, cut into pieces and eaten or placed under the tongue or in the cheek for absorption. Even used patches are attractive to substance misusers as some of the drug remains even after use. There is are perhaps hundreds of online sites where one can trade tips and information about the ways to get the most out of the drug in whatever form it is in.
Prescription Drug Abuse and the Prescription Opioid Abuse Index (POMI)

Prescription drug abuse means taking a prescription medication that is not prescribed for you, or taking it for reasons or in dosages other than as prescribed. Abuse of prescription drugs can produce serious health effects, including addiction and death. Commonly abused classes of prescription medications include opioids (for pain), central nervous system depressants (for anxiety and sleep disorders), and stimulants (for ADHD and narcolepsy).

Opioids include hydrocodone (Vicodin®), oxycodone (OxyContin®), propoxyphene (Darvon®), hydromorphone (Dilaudid®), meperidine (Demerol®), and diphenoxylate (Lomotil®).

Central nervous system depressants include barbiturates such as pentobarbital sodium (Nembuta®), and benzodiazepines such as diazepam (Valium®) and alprazolam (Xanax®). Stimulants include dextroamphetamine (Dexedrine®), methylphenidate (Ritalin® and Concerta®), and amphetamines (Adderall®).

Long-term use of opioids or central nervous system depressants can lead to physical dependence and addiction. Opioids can produce drowsiness, constipation and, depending on amount taken, can depress breathing. Central nervous system depressants slow down brain function; if combined with other medications that cause drowsiness or with alcohol, heart rate and respiration can slow down dangerously. Taken repeatedly or in high doses, stimulants can cause anxiety, paranoia, dangerously high body temperatures, irregular heartbeat, or seizures.

In 2009, approximately 7.0 million persons were current users of psychotherapeutic drugs taken nonmedically (2.8 percent of the U.S. population). This class of drugs is broadly described as those targeting the central nervous system, including drugs used to treat psychiatric disorders (NSDUH, 2009). The medications most commonly abused are listed on the chart below:
What is driving this high prevalence?

Multiple factors are likely at work:

- Misperceptions about their safety. Because these medications are prescribed by doctors, many assume that they are safe to take under any circumstances. This is not the case: prescription drugs act directly or indirectly on the same brain systems affected by illicit drugs; thus their abuse carries substantial addiction liability and can lead to a variety of other adverse health effects.

- Increasing environmental availability. Between 1991 and 2009, prescriptions for stimulants increased from 5 million to nearly 40 million, an 8-fold increase, and opioid analgesics increased from about 45 million to nearly 180 million, a 4-fold increase.

- Varied motivations for their abuse. Underlying reasons include: to get high; to counter anxiety, pain, or sleep problems; or to enhance cognition (although they may, in fact, impair certain types of cognitive performance).
NYS Controlled Substance Prescribing - 2009

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Number of Scripts</th>
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<tr>
<td>Hydrocodone</td>
<td>Lorcet, Norco, Vicodin</td>
<td>4,483,794</td>
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<td>Zolpidem</td>
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<td>Lorazepam</td>
<td>Ativan</td>
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<tr>
<td>Diazepam</td>
<td>Valium</td>
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</tbody>
</table>

With nonmedical use of opioids on the rise, it is important to develop methods of detection of those at risk for misuse of prescription narcotics. Knisely et al in their article in the *Journal of Substance Abuse Treatment* (2008 Vol 35 pp 380-386) report on a screening tool called the Prescription Opioid Misuse Index (POMI).

The POMI

The POMI initially was an eight item interview which was reduced to six items after further testing and analysis. It includes a question about pain relief to confirm that any increase in prescription use was not due to inadequate pain control.

1. Do you ever use MORE of your medication, that is, take a higher dosage, than is prescribed for you? Yes/ No
2. Do you ever use your medication MORE OFTEN, that is, shorten the time between dosages, than is prescribed for you? Yes/ No
3. Do you ever need early refills for your pain medication? Yes/ No
4. Do you ever feel high or get a buzz after using your pain medication? Yes/No

5. Do you ever take your pain medication because you are upset, using the medication to relieve or cope with problems other than pain? Yes/No

6. Have you ever gone to multiple physicians including emergency room doctors, seeking more of your pain medication? Yes/No

An affirmative answer to more than one question correctly classified an individual as an opioid misuser, with high sensitivity and specificity. The strengths of POMI include ease of administration by a nonphysician, clear criteria and brevity. This screen should be considered by all medical practices that prescribe medications for pain relief.

There are other screening tools for the detection of risk to misuse:

- **Prescription Drug use Questionnaire (PDOQ)**
  - Developed by Compton et al 1998
  - 42 items
  - Must be administered by a trained mental health professional
  - Time consuming

- **Screener and Opioid Assessment for Patients with Pain (SOAPP)**
  - Developed by Butler et al 2004
  - 14 items

- **Opioid Risk Tool (ORT)**
  - Developed by Webster 2005
  - Less than 10 minutes to take
  - Self Administered
The Neuroleptic Malignant Syndrome (NMS)

The neuroleptic malignant syndrome (NMS) is the combination of hyperthermia, rigidity and autonomic dysregulation that can occur as a serious complication of the use of antipsychotic medications. This syndrome was first delineated in 1960 by Jean Delay, MD. The syndrome can occur after any duration of treatment, though two-thirds of cases occur within the first week of using antipsychotic medications. The frequency of the syndrome has been variable with reports of 0.07 percent to 2.2 percent of patients taking antipsychotic medications. The mortality rate for NMS is difficult to determine due to reporting errors, but it is estimated to be between 10 - 20 percent. Mortality is generally highest in patients who develop severe muscle necrosis (cell breakdown and death).

Neuroleptic malignant syndrome can be seen with many of the antipsychotics, even the newer atypical ones such as: olanzapine, risperidone, paliperidone, aripiprazole, ziprasidone, amisulpride, quetiapine and to a lesser degree Clozapine.

The accepted mechanism whereby antipsychotics cause NMS is that they are dopamine D2 receptor antagonists (blockers) so that there is a decrease in dopamine receptor activation. D2 receptor blockade results in an elevated temperature set point and impairment of heat-dissipating mechanisms. Peripherally, antipsychotics lead to increased calcium release which can contribute to hyperthermia, rigidity, and muscle cell breakdown.

NMS is seen in more men than women and the incidence is higher in those patients younger than 40. The clinical features that make the diagnosis are:

- severe muscular rigidity – shuffling gait
- hyperthermia (elevated temperature)
- diaphoresis (sweating)
- dysphagia (difficulty swallowing)
- tremor
- incontinence
- autonomic instability - labile blood pressure and elevated heart rate
- pallor
- dysnea (shortness of breath)
- changes in the level of consciousness - delirium progressing to lethargy, stupor and coma
- leukocytosis (elevated white blood count)
- laboratory evidence of muscle injury - elevated creatine kinase (CK)

Symptoms should improve after the antipsychotic is stopped.
Various other medications cause conditions that are indistinguishable from NMS and likely involve similar pathophysiology. Some examples of these other medications include: metoclopramide, prochlorperazine, and promethazine.

Antipsychotics can cause a variety of reactions that can be confused with neuroleptic malignant syndrome. These reactions often occur with increasing medication dosages.

- neuroleptic-induced acute dystonia - an abnormal contraction or spasm of a group of skeletal muscles, often involving the head or neck
- neuroleptic-induced acute akathisia - motor restlessness, particularly involving the legs
- neuroleptic-induced tardive dyskinesia - involuntary, rhythmic movements starting with mouth movements
- neuroleptic-induced parkinsonism, or pseudoparkinsonism - presents with the classic triad of tremor, muscular rigidity, and akinesia (absence or loss of the power of voluntary motion)

Serotonin syndrome is very similar to neuroleptic malignant syndrome. The triad of (1) altered mental status, (2) autonomic dysfunction, and (3) neuromuscular abnormalities that occurs on exposure to serotonergic agents characterizes the serotonin syndrome. Selective serotonin reuptake inhibitors (SSRIs) - commonly used for treatment of depression and anxiety - are the most frequently used medications in this class. The serotonin syndrome can be distinguished from neuroleptic malignant syndrome in most cases by a detailed history of medication use with particular attention to recent dosage changes and the absence of severe rigidity.

The potential risk factors for neuroleptic malignant syndrome include the following:

- dehydration
- agitation
- exhaustion
- malnutrition
- organic brain syndromes
- nonschizophrenic mental illness
- lithium use
- past history of electroconvulsive therapy
- warm and humid environments
- inconsistent use of neuroleptics
- postpartum period

The most important treatment intervention is to discontinue all antipsychotics. In most cases, symptoms will resolve in 1 - 2 weeks. Neurolepticmalignant syndrome
precipitated by long-acting depot injections (intramuscular injections that results in a gradual release) of antipsychotics can last as long as a month.

The potential complications of neuroleptic malignant syndrome include the following:

- rhabdomyolysis (rapid breakdown of skeletal muscle)
- renal failure
- cardiac arrest
- infection
- aspiration
- respiratory failure
- seizure
- pulmonary embolism
- hepatic failure (loss of normal liver function)
- uncontrolled psychoses

Patients who have previously experienced episodes of neuroleptic malignant syndrome are at risk for recurrences. The risk of neuroleptic malignant syndrome recurrence is related to the time between an episode of neuroleptic malignant syndrome and restarting the antipsychotic medication.

If patients are rechallenged with antipsychotics within two weeks of an episode of neuroleptic malignant syndrome, 63 percent will have a recurrence. If more than two weeks has elapsed, only 30 percent will have a recurrence.

Eighty-seven percent of patients who develop neuroleptic malignant syndrome will be able to tolerate another antipsychotic at some point in the future.

Source: This FYI was adapted from a complete review that can be found at: http://emedicine.medscape.com/article/288482-overview
Drugged Driving

The dangers associated with drunk driving has been publicized and legislated against only in the last 25 years and as a result there has been a decrease in the numbers of people killed or injured as a result of drunk driving. There are similar dangers being noted with driving under the influence of drugs and medications.

The principal concern regarding drugged driving is that driving under the influence of any drug that acts on the brain could impair one's motor skills, reaction time, and judgment. Drugged driving, like drunk driving, is a public health concern because it puts not only the driver at risk, but also passengers and others who share the road.

Despite these acknowledged concerns, drugged driving laws have lagged behind alcohol legislation, in part because of limitations in the current technology for determining drug levels, and resulting impairment. For alcohol, detection of its blood concentration (BAC) is relatively simple and concentrations greater than .08 percent have been shown to impair driving performance. Thus, 0.08 percent is the legal limit in this country. For illicit drugs, there is no agreed upon limit for which impairment has been reliably demonstrated. Determining current drug levels can be difficult, since some drugs linger in the body for a period of days or weeks after initial use.

How Many People Take Drugs and Drive?

According to the National Highway and Safety Administration's (NHTSA) 2007 National Roadside Survey, more than 16 percent of weekend, nighttime drivers tested positive for illegal, prescription, or over-the-counter medication. Greater than 11 percent tested positive for illicit drugs.

According to the 2008 National Survey on Drug Use and Health, an estimated 10 million people age 12 and older reported driving under the influence of illicit drugs during the year prior to being surveyed. This corresponds to 4 percent of the population age 12 and older, similar to the rate in 2007 (4.2 percent), but lower than the rate in 2002 (4.7 percent). In 2008, the rate was highest among young adults age 18 to 25 (12.3 percent).

Driving under the influence of an illicit drug or alcohol was associated with age. In 2008, an estimated 7.2 percent of youth age 16 or 17 drove under the influence. This percentage steadily increased with age to reach a peak of 26.1 percent among young adults age 21 to 25. Beyond the age of 25, these rates showed a general decline with increasing age.

Also in 2008, among persons age 12 and older, males were nearly twice as likely as females (16.0 percent versus 9.0 percent) to drive under the influence of an illicit drug or alcohol in the past year.

A number of studies have examined illicit drug use in drivers involved in motor vehicle crashes, reckless driving, or fatal accidents. For example:
• One study found that about 34 percent of motor vehicle crash victims admitted to a Maryland trauma center tested positive for “drugs only”; about 16 percent tested positive for “alcohol only.” Approximately 9.9 percent (or 1 in 10) tested positive for alcohol and drugs, and within this group, 50 percent were younger than age 18 (4. Walsh JM, Flegel R, Cangianelli LA, Atkins R, Soderstrom CA, Kerns TJ. Epidemiology of alcohol and other drug use among motor vehicle crash victims admitted to a trauma center. Traffic Inj Prev 5(3):254 - 260, 2004.) Although it is interesting that more people in this study tested positive for “drugs only” compared with “alcohol only,” it should be noted that this represents one geographic location, so findings cannot be generalized. In fact, the majority of studies among similar populations have found higher prevalence rates of alcohol compared with drug use.

• Studies conducted in several localities have found that approximately 4 to 14 percent of drivers who sustained injury or died in traffic accidents tested positive for delta-9-tetrahydrocannabinol (THC), the active ingredient in marijuana (6. Ramaekers JG, Berghaus G, van Laar M, Drummer OH. Dose related risk of motor vehicle crashes after cannabis use. Drug Alcohol Depend 73(2):109â€“119, 2004.)

• The highest rates of driving under the influence of illicit drugs in the past year among adults aged 18 or older were in the District of Columbia (7.0 percent), Rhode Island (6.8 percent), Massachusetts (6.4 percent), Montana (6.3 percent), and Wyoming (6.2 percent) (based on 2004, 2005, 2006 SAMHSA).

**Teens and Drugged Driving**

According to the Centers for Disease Control and Prevention, vehicle accidents are the leading cause of death among young people age 16 to 19. It is generally accepted that because teens are the least experienced drivers as a group, they have a higher risk of being involved in an accident compared with more experienced drivers. When this lack of experience is combined with the use of marijuana or other substances that impact cognitive and motor abilities, the results can be tragic.

• The 2007 State of Maryland Adolescent Survey indicates that 11.1 percent of the State’s licensed adolescent drivers reported driving under the influence of marijuana on three or more occasions and 10 percent reported driving while using a drug other than marijuana (not including alcohol).

• Results from NIDA's Monitoring the Future survey indicate that, in 2008, more than 12 percent of high school seniors admitted to driving under the influence of marijuana in the 2 weeks prior to the survey.

**Older Drivers and Drugged Driving**

In a cohort study of nearly 28,000 Medicare+Choice enrollees cared for by a multispecialty practice (an ambulatory clinic setting) during a 12-month study period between 1999 and 2000, researchers found that 75 percent of the sample received prescriptions for 6 or more prescription drugs (Gurwitz, Field, Harrold, Rothchild,
Debellis, Seger, Cadoret, Fish, Garber, Kelleher, and Bates, 2003). Forty-nine percent of the sample was prescribed medications in four or more categories.

A few studies examine multiple medication use. However, there is a dearth of research on the effects of combinations of specific medications or even combinations of drug classes on driving ability per se. However, in one recent and comprehensive pharmacy database analysis of multiple medication use (LeRoy, 2004), higher percentages of crash-involved drivers were prescribed two or more prescriptions than non crash-involved drivers. The most frequently appearing drug combinations (in descending order of frequency) in the group of crash-involved drivers age 50 and older were:

- Narcotics + Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).
- Skeletal Muscle Relaxants + NSAIDs.
- Narcotics + Skeletal Muscle Relaxants.
- Narcotics + Skeletal Muscle Relaxants + NSAIDs.
- Narcotics + Antibiotics.
- Gastric Acid Secretion Reducers + Narcotics.
- Anti-Anxiety Drugs + Narcotics.
- Serotonin Reuptake Inhibitor (SSRI) Antidepressants + Narcotics.
- Narcotics + NSAIDs + Antibiotics.

Why is Drugged Driving Hazardous?

Drugs acting on the brain can alter perception, cognition, attention, balance, coordination, reaction time, and other faculties required for safe driving. The effects of specific drugs of abuse differ depending on their mechanisms of action, the amount consumed, the history of the user, and other factors.

Drug Use and Driving

Marijuana is the most prevalent illegal drug detected in impaired drivers, fatally injured drivers, and motor vehicle crash victims. Other drugs also implicated include benzodiazepines, cocaine, opiates, and amphetamines. It is recommended that testing should be done for the 6 most common classes of drugs other than alcohol among individuals involved in motor vehicle accidents. These are marijuana; benzodiazepines and other tranquilizing agents; opioids; stimulants such as amphetamines, cocaine, methamphetamine, and methylenedioxymethylamphetamine; antidepressants; and antihistamines.

Finally drug combinations make a difference in the effect. Drug combinations (called poly-drug use) may cause one of three reactions: additive, synergistic or antagonistic.
• **Additive** Effects occur when drug combinations produce an effect that is like simple addition, such as the equation: $1+1=2$.

• **Synergistic** Effects occur when drug combinations produce an effect that is greater than the sum of the effects of the two drugs, such as the equation: $1+1=3$.

• **Antagonistic** Effects occur when a drug combination produces an effect that is less than the sum of the effects of the drugs acting alone, such as the equation: $1+1=1$ or $1+1=0$.

**Marijuana**

THC affects areas of the brain that control the body’s movements, balance, coordination, memory, and judgment, as well as sensations. Because these effects are multifaceted, more research is required to understand marijuana's impact on the ability of drivers to react to complex and unpredictable situations. Delta (9)-tetrahydrocannabinol (THC), the most important psychoactive substance in cannabis, is frequently detected in blood from apprehended drivers suspected for drugged driving. Both experimental and epidemiological studies have demonstrated the negative effects of THC upon cognitive functions and psychomotor skills. These effects could last longer than a measurable concentration of THC in blood. Culpability studies have recently demonstrated an increased risk of becoming responsible in fatal or injurious traffic accidents, even with low blood concentrations of THC. It has also been demonstrated that there is a correlation between the degree of impairment, the drug dose and the THC blood concentration. It is very important to focus on the negative effect of cannabis on fitness to drive in order to prevent injuries and loss of human life and to avoid large economic consequences to the society. KhiabaniHZ et al, Tidsskr Nor Laegeforen. 2007; 127(5):583-4.

What we know:

• A meta-analysis of approximately 60 experimental studies, including laboratory, driving simulator, and on-road experiments, found that behavioral and cognitive skills related to driving performance were impaired in a dose-dependent fashion with increasing THC blood levels (Berghaus G, Sheer N, Schmidt P. Effects of Cannabis on Psychomotor Skills and Driving Performance - A Meta-Analysis of Experimental Studies. In: Kloeden CN and McLean AJ, eds. Proceedings of the 13th International Conference on Alcohol, Drugs and Traffic Safety. Adelaide, Australia: The University of Adelaide, NHMRC Road Accident Research Unit, pp. 403 - 409, 1995.)

• Evidence from both real and simulated driving studies indicates that marijuana can negatively affect a driver's attentiveness, perception of time and speed, and the ability to draw on information obtained from past experiences.

• A study of over 3000 fatally-injured drivers in Australia showed that when marijuana was present in the blood of the driver they were much more likely to be at fault for the accident. And the higher the THC concentration, the more likely they were to be culpable (Drummer OH, Gerostamoulos J, Batziris H, Chu M,

- Research shows that impairment increases significantly when marijuana use is combined with alcohol. Studies have found that many drivers who test positive for alcohol also test positive for THC, making it clear that drinking and drugged driving are often linked behaviors (National Highway Traffic Safety Administration. Marijuana and alcohol combined severely impede driving performance. Ann Emer Med 35(4):398 - 399, 2000)

- When combined with sedatives and opiates, marijuana can cause an increase in anxiety and even hallucinations, along with an increase in heart rate and blood pressure when used with amphetamines. On the other hand, effects are somewhat unpredictable when marijuana is combined with stimulants, such as nicotine, caffeine, amphetamines, and cocaine.

Prescription drugs

Many medications (e.g., benzodiazepines and opiate analgesics) act on systems in the brain that could impair driving ability. In fact, many prescription drugs come with warnings against the operation of machinery - including motor vehicles - for a specified period of time after use. When prescription drugs are taken without medical supervision (i.e., when abused), impaired driving and other harmful reactions can also result.

Opioids

Some of the opioids share with alcohol and cannabis an acute intoxicating effect, although the sedative effect is more pronounced. Acute administration of heroin causes euphoria in many users, although other opioids such as methadone do not have this effect in tolerant individuals. The extent of euphoria is also affected by route of administration. As is found with cannabis, some naive users report unpleasant feelings with opiate use, specifically nausea and dysphoria. All opioids are CNS depressants and as such can reduce level of consciousness and cause sleep.

The literature on the effects of opiates on driving and other exacting skills is not well developed. A maintenance dose in a tolerant user may produce little psychomotor or cognitive impairment. A heroin user who has reached a stage of "nodding" is in no condition to drive a car, but will probably have little inclination to do so. One study showed that the driving-related skills of persons maintained on stable doses of methadone were not impaired when assessed on a laboratory task that is sensitive to the effects of alcohol (Chesher, Lemon, Gomal and Murphy, 1989).

Stimulants

Stimulant drugs, such as caffeine, amphetamines and cocaine, may increase alertness, but this does not mean they improve driving skills. The tired driver who drinks coffee to stay awake on the road should be aware that the stimulant effect can wear off suddenly, and that the only remedy for fatigue is to pull off the road and sleep. Amphetamines do
not seem to affect driving skills when taken at medical doses, but they do make some people overconfident, which can lead to risky driving. Higher doses of amphetamines often make people hostile and aggressive.

People who use cocaine are also likely to feel confident about their driving ability. But cocaine use affects vision, causing blurring, glare and hallucinations. “Snow lights” - weak flashes or movements of light in the peripheral field of vision - tend to make drivers swerve toward or away from the lights. People who use cocaine may also hear sounds that aren’t there, such as bells ringing, or smell scents that aren’t there, such as smoke or gas, which distract them from their driving.

Additive effects are noted when cocaine is combined with over-the-counter products, such as diet pills or antihistamines. Cocaine taken with psychotropics, especially antidepressants, can be extremely detrimental. A person who has extremely high blood pressure and uses cocaine may suffer from a stroke or heart attack. Some users combine cocaine with alcohol and sedatives to cushion the "crash" or feeling of depression and agitation that sometimes occurs as the effects of cocaine wear off. Further research indicates that additive and antagonistic effects can be produced when cocaine is mixed with alcohol. If cocaine is used in high doses, as in the case of overdose, alcohol will probably have an additive effect on the symptoms that eventually contribute to death.

**Amphetamines**

The use of amphetamines can interfere with concentration, impair vision, and increase the driver's tendencies to take risks. Amphetamines should never be taken with a class of antidepressants known as MAO inhibitors, because of potential hypertensive crisis. Amphetamine users sometimes use marijuana and depressant drugs in order to avoid the adverse side effects of the "crash," therefore creating multiple drug effects.

**Sedatives**

The use of sedatives produces drowsiness, a lack of coordination, altered perceptions, memory impairment, poor control of speech, and slower reaction time. Effects on driving include poor tracking, difficulty in maintaining lane position, and neglecting roadside instructions. When sedatives are combined with alcohol or other central nervous system depressants, synergistic effects may be produced, which may be fatal. Alcohol increases the absorption of benzodiazepines, slows their break down in the liver and can cause cardiovascular and respiratory depression. People who take stimulants sometimes take tranquilizers to off set agitation and sleepiness.

The acute intake of benzodiazepines is followed by concentration-dependent deterioration of performance in controlled experimental studies. Whether this is true in a population of benzodiazepine users is uncertain. In Norway physicians examine and take blood samples from nearly all suspected drivers. The blood concentration of benzodiazepines was the only characteristic which was related to driving impairment.
This indicated a drug-concentration related effect of benzodiazepines on performance (BramnessJG et al Drug Alcohol Depend. 2002; 68(2):131-41).

**Hallucinogens**

The effects of hallucinogenic drugs, such as LSD, ecstasy, mescaline and psilocybin, distort perception and mood. Driving while under the influence of any of these drugs is extremely dangerous.

**Recidivism** is a major problem in the prevention of DUI offenses. It is suggested that impairing substances used by drivers may relate to a higher risk of recidivism. Drivers with drugs only or a combination of drugs and alcohol had a significantly higher re-arrest rate than drivers with alcohol alone. Drivers with amphetamines only had the highest re-arrest rates. Findings of benzodiazepine and opioids alone did not increase the risk of re-arrest in the long run. Young age, male sex, high blood alcohol level, and arrest during the nighttime and during weekdays constituted a higher risk for re-arrest. The conclusion of the Impinen study was that a third of those suspected of driving under the influence of alcohol and/or drugs are rearrested within 15 years. Drugs, especially amphetamines, are a risk factor for faster re-arrest (ImpinenA et al Traffic Inj Prev. 2009; 10(3):220-6)

**Some Recommendations to Consider:**

- It is important for physicians to advise their patients of the potentially impairing effects of benzodiazepines and opioids, particularly in relation to drowsiness and sedation, and the implications of these effects on driving skills such as reaction time, attention and vigilance.

- An extensive history of all the patient's medication should be taken. This includes prescribed, over-the-counter medications and illicit drugs. Particular attention should be given where drugs have a sedating effect (as the effects may be synergistic) or may alter the pharmacokinetics of the opioid or benzodiazepine resulting in an increase in blood levels (e.g. fluvoxamine - Luvox can double blood methadone levels).

- Remember some patients may self-medicate in excess of the prescribed dosage.

- Patients should avoid driving for up to four weeks while stabilizing on benzodiazepine or opioid dosing regimens

- Some states (Arizona, Georgia, Indiana, Illinois, Iowa, Michigan, Minnesota, Nevada, N.Carolina, Ohio, Pennsylvania, Rhode Island, Utah, Virginia, and Wisconsin), have passed "per se" laws—in which it is illegal to operate a motor vehicle if there is any detectable level of a prohibited drug, or its metabolites, in the driver's blood. Other state laws define "drugged driving" as driving when a drug "renders the driver incapable of driving safely" or "causes the driver to be impaired."

- In addition, 44 states and the District of Columbia (NYS is included) have implemented Drug Evaluation and Classification Programs, designed to train
police officers as Drug Recognition Experts. Officers learn to detect characteristics in a person’s behavior and appearance that may be associated with drug intoxication. If the officer suspects drug intoxication, a blood or urine sample is submitted to a laboratory for confirmation.

- In Europe, drug labels include a green, yellow, or red code that indicates whether it is safe to drive when taking a particular agent.

01/2011
Bath Salts

Not your average bath salts that you pour into the bathtub to soak in after a hard day to relax - these so-called bath salts are intended to be snorted, smoked or injected. “Bath salts" have hit the market and can be one or two drugs - Mephedrone or Methylenedioxypyrovalerone (MDPV). Below is a summary of each.

**Methylenedioxypyrovalerone (MDPV)**

MDVP is a psychoactive drug with stimulant properties. It is reported that it has four times the potency of Ritalin. It is not FDA approved and is only a controlled, scheduled drug in some states. It is also known as MDPK, Magic, Super Coke and PV.

In 2010 it was reportedly sold as a legal drug alternative and marketed in the United States as "bath salts" in gas stations and convenience stores, similar to the marketing for Spice and K2 as incense. MDPV was then going under the street names of Cloud 9, Ivory Wave, Ocean, Charge Plus, White Lightning, Scarface, Hurricane Charlie, Red Dove and White Dove.

The substance appears as a pure white to light-brown crumbly powder with a slight starchy odor. Acting like a stimulant, its acute effects include: rapid heartbeat, increase in blood pressure, sweating, euphoria, increase alertness, increased wakefulness, anxiety, agitation, and perception of a diminished requirement for food and sleep. Routes of use includes: oral consumption, insufflation, smoking, rectal administration and intravenously.

The effects have a duration of roughly 3 to 4 hours. The elevated heart rate and blood pressure can last for 6 - 8 hours. High doses have been observed to cause intense, prolonged panic attacks in stimulant-intolerant users, and there are anecdotal reports of psychosis from sleep withdrawal and dependence at higher doses or more frequent dosing intervals.

Extended binges have caused significant withdrawal symptoms such as: depression, lethargy, headache, anxiety, lightheadedness, weakness, bruxism (teeth grinding, jaw clenching), kidney pain, abdominal pain and bloodshot eyes. The usual withdrawal can subside in 4 - 8 hours.

**Mephedrone**

(fom a summary of the 2010 Europol– European Monitoring Center for Drugs and Drug Addiction (EMCDDA) Joint Report on Mephedrone)

Mephedrone is the common name for 4-methylmethcathinone. Mephedrone is a psychoactive substance which is a cathinone derivative. Cathinone is a monoamine alkaloid found in the shrub Catha edulis(khat) and is chemically similar to ephedrine and some amphetamines. Cathinone derivatives are closely related to the phenethylamine
family of psychostimulants. Cathinone and its analogs are considered illegal drugs in the United States.

Mephedrone is also known as MMC or 4-MMC (which is an abbreviation for 4 methyl -methcathinone), M-CAT or MMCAT.

Mephedrone hydrochloride salt is a white powder, while its free base is a yellowish liquid at ambient temperature. Mephedrone is sold as its stable, water-soluble, white or lightly colored hydrochloride salt.

Mephedrone is commercially available from chemical suppliers on the Internet where it can be purchased in bulk. The purity of mephedrone offered on the internet is very high — reportedly over 99 percent.

Mephedrone has been identified in 'ecstasy'-like tablets, but it is also sold as a “legal high” - a legal alternative to amphetamine and cocaine. On the Internet, mephedrone is advertised as a research chemical, bath salts, for botanical research, plant food, and plant feeder; often with a note indicating that it is not for human consumption in order to circumvent potential control mechanisms. There is often no indication of the presence of psychoactive substances in the list of ingredients of the marketed products. There are, however, online shops which are more explicit about the actual usage of mephedrone. Internet sites targeting recreational drug users offer mephedrone powder in retail quantities - for example - 1 g, 5 g, and 10 g up to 200 g. Furthermore, it can also be bought in bulk from Asian-based chemical laboratories (China).

In March 2010, an Internet audit identified 78 online shops, of which 39 sold mephedrone in only retail quantities (less than 200 grams), while 38 sold it both in retail and bulk quantities.

There are no formal pharmacokinetic and pharmacodynamic studies on mephedrone. There are no published formal studies assessing the psychological or behavioral effects of mephedrone in humans. In addition, there are no animal studies on which to base an extrapolation of potential effects. Therefore psychological and behavioral effects related to mephedrone use are based on users’ reports and clinical reports of acute mephedrone toxicity. From the reported clinical effects seen in patients with mephedrone toxicity and effects reported on user discussion forums, it appears that mephedrone has similar effects to amphetamine derivatives.

The desired psychological and behavioral effects reported by users include:

- euphoria
- general stimulation
- enhanced music appreciation
- elevated mood
- decreased hostility
• improved mental function
• mild sexual stimulation (reported in 60 percent of mephedrone users)

Overall, these effects are similar to those seen in other stimulant drug use (MDMA, amphetamines, cocaine).

Users report on Internet forums that desired effects are typically seen within 15–45 minutes of oral ingestion. There are some reports of slower onset of action when mephedrone is taken orally on a full stomach. Following nasal insufflation, onset is reported within a few minutes and with peak effects within 30 minutes. Users report that the effects last approximately 2–3 hours and therefore that they may consume multiple doses during a session to prolong the duration of the desired effects. Reports from intravenous mephedrone users suggest that the high lasts approximately 10–15 minutes with an overall duration of desired effects of approximately 30 minutes.

Symptoms of use reported by users on Internet forums include: numbness, lack of tactile sensitivity, loss of appetite, insomnia, increased mean body temperature (‘mephedrone sweat’), decrease in mean body temperature, bruxism, elevated heart rate and blood pressure, chest pain, nausea and vomiting, painful joints, discoloration of extremities/joints, abdominal pain, painful nasal drip with presence of blood, light headedness and dizziness, tremors, convulsions, headaches, cravings, nightmares, loss of concentration and memory loss, anxiety, depression, hallucinations, paranoia, fatigue and respiratory difficulties.

There are reports, particularly after intravenous use, of more severe psychological and behavioral effects. These include:

• delusional parasitiosis leading to scratching and gauging of the skin particularly of the face, neck and arms
• Parkinson-like twitching of limbs
• paranoia
• suicidal ideation
• severe insomnia

Data is available on 31 cases of acute toxicity associated with self-reported mephedrone use in London since January 2009. The most common clinical symptoms/signs on presentation were:

• sixteen (51.6 percent) reported agitation
• eight (25.8 percent) presented with palpitations
• six (19.4 percent) presented with vomiting
• three (9.7 percent) reported a self-limiting pre-hospital seizure
• one (3.4 percent) presented with bruxism.
• one (3.4 percent) presented with a headache.
Twenty-five (80.6 percent) patients were discharged either directly from the emergency department or the short-stay observation ward. These patients required either a period of observation prior to discharge and/or symptom control medications. Four (12.9 percent) patients required the use of benzodiazepines for the management of agitation on presentation to the hospital. Of the six patients who were admitted to hospital, four were admitted for observation/management on a general internal medicine ward and two (6.4 percent of all presentations) required admission to the intensive care unit. All patients survived to leave hospital with no long-term sequelae on discharge.

There has been only one confirmed death related solely to mephedrone. This case was in Sweden and was an 18 year old female who reported use of mephedrone and cannabis. Toxicological screening of blood and urine revealed the presence of mephedrone only (the mephedrone concentration was not reported), with no other drugs or alcohol detected.
Seroquel (Quetiapine) Misuse

Quetiapine which is marketed by AstraZeneca as Seroquel has been approved for the treatment of schizophrenia and acute episodes of bipolar disorder. It has also been used as an augmentor for the maintenance treatment of depression.

The common side effects include: sluggishness, fatigue, dry mouth, sore throat, dizziness, abdominal pain, constipation, upset stomach, sudden drop in blood pressure upon standing, inflammation or swelling of the sinuses or pharynx, increased appetite, and weight gain. However, it is the most common side effect - somnolence (the state of near sleep) - that has caused most of the misuse of this medication.

Quetiapine is not a controlled substance, though reports have emerged of misuse through the crushing and snorting of tablets, to the use of this medication intravenously either alone or in combination with cocaine. The combined use has been referred to as a “Q-Ball”. Other names that have been used for the medication alone are: “quell”, “snoozeberries”, and “Susie-Q”.

Misuse has also been reported in some jail and prison systems where psychotic symptoms were faked in an attempt to obtain this medication. Olanzapine (Zyprexa) has also been reported being sought for its sedative qualities.

Some facts to consider with normal use of Quetiapine:

- It is important to also be aware of false positive urine drug screens for methadone when quetiapine is used. Quetiapine is extensively metabolized by the cytochrome P450 3A4 isoenzyme, resulting in 2 major metabolites (sulfoxide and the carboxylic acid parent metabolite). Of a given dose, 73 percent is metabolized and excreted in the urine. Therefore, it is postulated that these renally excreted metabolites could be structurally similar enough to the tertiary structure of methadone to induce a cross-reactivity-related artifact in the methadone urine drug screen.

- Risk of Suicidality: A small number of children, teenagers, and young adults (up to 24 years of age) who took antidepressants ('mood elevators') such as quetiapine during clinical studies became suicidal (thinking about harming or killing oneself or planning or trying to do so). Children, teenagers, and young adults who take antidepressants to treat depression or other mental illnesses may be more likely to become suicidal than children, teenagers, and young adults who do not take antidepressants to treat these conditions. However, experts are not sure about how great this risk is and how much it should be considered in deciding whether a child or teenager should take an antidepressant. Children younger than 18 years of age should not normally take quetiapine, but in some cases, a doctor may decide that quetiapine is the best medication to treat a child's condition (PubMed Health - U.S. National Library of Medicine, National Institutes of Health – March 2010)
• No matter what your age, before you take an antidepressant, you should talk to your doctor about the risks and benefits of treating your condition with an antidepressant or with other treatments. You should also talk about the risks and benefits of not treating your condition. Talk to your doctor about your condition, symptoms, and personal and family medical history (including history of substance use disorders). You and your doctor will decide what type of treatment is right for you.

Taking medications as prescribed by doctors is a lot different than self medicating with alcohol and drugs to suppress feelings or avoid reality. However, it is important to remember that many patients with alcohol dependence or substance use disorders may react differently to medication; whether it's a prescribed medication, an illegal street drug, or an over the counter medicine.
Tips on Buprenorphine Use

The SAMHSA Treatment Improvement Protocol, TIP 40, Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction, was written before buprenorphine was available. There have been some significant changes that have occurred in the way buprenorphine is used since that time.

The only current use of Subutex should be for pregnancy and if there is an allergy to naloxone.

- Some programs that have controlled environments (inpatient rehabs for example), may choose to use the generic form to reduce costs.

When performing office induction

- The original period of observation as noted in the TIPS may be too long and many physicians are using 45 minutes to one hour
- The suggested maximum dose for the first day is 8 mg though some physicians have used higher doses
- The patients are not seen everyday and a take home prescription can be given. Consider the option of calling the patient, evaluating how they are doing and changing the dose if needed.

Home induction was not considered in the original TIPS

- This method can be used if telephone contact for the first three days at a minimum is available
- One must remember that the patient must be in withdrawal (at least a few physiologic signs) before starting buprenorphine
- The physician must be available 24/7
- The usual first dose is 4 mg

Transferring from methadone to buprenorphine

- Consider the maximum dose of methadone to be 20 - 25 mg
- Due to methadone metabolism, one cannot start buprenorphine at 24 hours after stopping methadone. 48 hours after the methadone dose may be a starting point and some may need 72 hours or longer before exhibiting withdrawal signs and symptoms.
- Stabilization dosing:
  - 32 mg is too high for the vast majority of patients and 24 mg may be the upper limit
The Pregnant patient

- If on methadone, no reason to switch off
- If on heroin, consider buprenorphine as your first choice (not yet FDA approved, but may be useful in those cases where methadone is not available or patient does not want methadone maintenance therapy)
- Since not FDA approved, documentation for rationale in the chart is necessary
  - Excellent article in JAMA describing the Mothers Study (363;24 Dec 9, 2010)

Note: A formal presentation and discussion of these points will be forthcoming on the Institute for Research, Education and Training in Addiction (IRETA) website.
Predictors for Efficacy of Naltrexone Treatment in Alcohol Dependence: Sweet Preference

Many studies have shown that naltrexone, by reducing relapses to heavy drinking, is an effective treatment for alcohol dependence. Can we predict which patient is likely to do best on naltrexone? Better responses have been seen in those patients with: significant alcohol craving, a positive family history of alcohol dependence, use of other addicting substances, the 118G sequence for the opiate mu receptor (the mu opioid receptor is centrally involved in the development of the addictive diseases) and a preference for sweets.

The rational for sweet preference is that sweet preference is a measure of opioid reinforcement and naltrexone works by blocking opioid reinforcement. Thus, a patient who is particularly sensitive to the reinforcing effects of sweet solutions may have an opioid system that produces greater reinforcement from alcohol and thus greater therapeutic benefit from naltrexone.

In a study by E. Laaksonen et al in Alcohol and Alcoholism (Jan - Feb 2011 46 (1), the researchers sought to evaluate the possible associations between sweet preference and the efficacy of naltrexone treatment in alcohol dependence.

78 patients underwent sweet testing using 50 mg of naltrexone daily for 12 weeks and then as needed for 20 weeks (along with behavioral therapy).

Sweet testing preference was conducted using six different concentrations of sucrose solution given in random order. The patients sipped the solution and then spit it out and rinsed their mouth with distilled water to then proceed to the next solution.

The sweet preference was calculated as the correlation between the ranking of the sucrose concentrations and the preference for that solution. A sweet score of 1.00 indicated a perfect correlation with the stronger solutions being preferred over the weaker ones.

In the patients who were treated with naltrexone, lower sweet scores significantly predicted more relapses to heavy drinking during the study period. This finding is consistent with research that shows that during treatment without naltrexone, patients with alcohol dependence classified as sweet-likers at baseline are less likely to succeed in treatment.

**Conclusion:** Sweet preference has a strong correlation to treatment outcomes with naltrexone, and sweet preference might be used as a predictor for better treatment results in alcoholics.
Combination Medications for the Treatment of Tobacco Dependence: Promising Combinations

The use of multiple nicotine patches or multiple nicotine replacement therapies (NRT) is well described for the treatment of tobacco dependence. The combination of bupropion (Zyban) and NRT’s is also well researched and gives abstinence results that are better than each single therapy when not combined. NRT cannot be used with varenicline (Chantix), so that varenicline has been a single use medication until the recent work of Ebbert et al in the publication *Nicotine and Tobacco Research* (2009).

Ebbert and his colleagues went under the premise that varenicline and bupropion sustained release are both safe and effective for the treatment of tobacco dependence and that each has a different mechanism of action.

- Varenicline is a partial agonist effecting partial receptor stimulation and competitive inhibition at the alpha4-beta2 neuronal nicotinic acetylcholine receptor.
- Buproprion is thought to work by blocking the reuptake of dopamine and norepinephrine in the reward center.

They combined the use of these two medications to see whether they could observe an increase in long-term smoking abstinence.

The study population averaged about one pack per day of cigarette consumption and smoked for an average of 30 years. The patients were given 1.0 mg of varenicline twice a day along with 150 mg of bupropion twice a day. The medications were given for 12 weeks. **Abstinence rates were 71 percent at 3 months and 58 percent at six months** (Abstinence was defined by: self report of smoking abstinence in the last 7 days and expired carbon monoxide less than or equal to 8 ppm.).

There was a four pound mean weight change over the first few weeks and the mean at six months for those who stopped smoking was about nine pounds. The most common side-effects were sleep disturbance (26 percent) and nausea (24 percent). Sleep disturbance was described as difficulty initiating or maintaining sleep and vivid dreams. It should be noted that sleep disturbances are part of the diagnostic criteria of nicotine withdrawal. There was not an increase in depressive symptoms or suicidal ideation reported. It appeared that the combination of medications decreased craving but did not decrease withdrawal scores over the first two weeks.
Kratom Abuse

Kratom is a medicinal plant that is grown in Southeast Asia with Thailand and Malaysia being the main harvesting areas. Kratom, which is a member of the Mitragyna plant family, is in the same family as coffee and the psychoactive plant Psychotria viridis. It is processed in a similar fashion to cannabis, whereby the leaves are dried and then made into a powder or oily resin. Kratom has been around for nearly 10 years, but only in the last year or two has it attracted widespread attention. Common names include Kratom, Ketum, Kakuam, Ithang and Thom.

Kratom powder or leaves can be made into a tea preparation, placed in capsules for oral ingestion or smoked. The high can last two to three hours and is dose dependent (three to five grams of crushed Kratom leaf or a half teaspoon of Kratom 15X powdered extract).

Symptoms of Kratom intoxication include:

- Pupil reaction to light- slow at doses of five grams or higher
- Pulse- near normal
- Blood pressure- near normal
- Body temperature- near normal
- Pupil size- near normal (constriction in high doses)

Kratom's area of action is believed to be the delta and mu opiate receptors. Mitragynine is the major alkaloid found in Kratom, 7-hydroxymitragynine is a minor alkaloid in Kratom that exhibits opiate-like analgesic effects that are similar or greater than morphine. Kratom has a biphasic effect with initial exhilaration followed by a sedating phase. The effects described as relaxing, anxiety reducing, and euphoric are most likely attributable to Kratom's activity at the delta and mu opiate receptors. There have been reports of use of Kratom for the treatment of the opiate withdrawal symptoms. One can postulate that the use of this drug could lead to an opiate-like dependence. Side effects, although rare, may include dry mouth, increased or decreased urination, loss of appetite, and nausea or vomiting. Heavy use can result in a prolonged sleep.

Marketing and control are a significant issue with Kratom:
Like Salvia divinorum, Kratom is considered a dietary supplement. It is not a controlled substance; it is legal to possess. Head shops and Internet Kratom stores are experiencing brisk sales of its various Kratom products.

Kratom is exhibitive of an emerging trend that bypasses modern toxicological monitoring. With the emergence of K2 (Spice) and bath salts as drugs of abuse, Kratom's popularity has surged.
The New “Designer” Drugs

A new group of “designer drugs” has hit the US market in an attempt to bypass laws for the sales or possession of illicit drugs. This FYI is an overview of these new drugs.

This group includes a wide range of products from natural plant origins to semi-synthetic and synthetic compounds. The compounds mimic psychoactive effects of illicit drugs of abuse but are claimed to be legal to sell, possess and use. These new compounds come in many formulations: powder, crystals, tablets, capsules, liquids, pre-rolled joints, smoking blends, and herbal mixtures. The compounds can be purchased on-line or at “head”, “smart”, “fun”, or “coffee” shops and are advertised as: air fresheners, herbal incenses, bath salts, plant fertilizer, collectibles and chemical reagents. Many of these products are named to refer to illegal street drugs such as CoCo Night, Speedway and Snow Blow.

There are three categories that we will review:

- synthetic Cannabinoids (“spice”)
- stimulants
- hallucinogens

**Synthetic Cannabinoids “Spice” Products:**

- available since 2004
- package information usually states it is of plant origin
- The plant material really acts as a dilutent for the synthetic compounds.
- The material is smoked, drank as a “tea” infusion or taken orally.
- Street names include: Spice, Aroma, Chill Out, Chill Zone, Fusion, K2, or Zen, among other names specific to the locale.
- The synthetic compounds found in these products include:
  - Naphthoyindoles (JWH-015, JWH-018, JWH-019, JWH-073, JWH-122, JWH-200, JWH-210, JWH387, JWH-398)
    - JWH-073 has been detected in 70 percent of the products on the market
    - JWH-018 has been detected in 60 percent of the products on the market
  - Phenylacetylindoles
  - Cyclohexylphenols
  - Benzoylindoles
  - Classic cannabinoid compounds
• Flavors, organic compounds of fatty acids and preservatives, have also been found in these products.
• The synthetic cannabinoids:
  o mimic delta-9-THC (the primary psychoactive ingredient in marijuana)
  o are lipid soluble (can pass through cell membranes)
  o Have effects one can see after smoking (although there have been few human studies): sedation, dry mouth, hot flush, burning eyes, dilated pupils, increase in heart rate but no increase in blood pressure and tremors. There have been a few cases of physical dependence on this class with resulting withdrawal signs and symptoms (tremors, insomnia, nightmares, palpitations, headache, diarrhea and nausea/vomiting).

**Stimulants** - The psychostimulant class of these compounds include synthetics that mimic amphetamine or ecstasy-like activity. There is little information on the pharmacologic properties of these compounds. The main four classes of this group include:

• Beta-Keto Amphetamine (mephedrone, methylon)
• 2,5,-Dimethoxy amphetamine
• 2,5,-Dimethoxy phenethylamine
• Piperazines (BZP, TFMPP, MeOPP, mCPPP, pFPP)

**BZP or benzylpiperazine:**

• available for greater than 10 years
• used as a “recreational” drug or to increase alertness and overcome sleepiness
• capsules contain 50 - 200 mgs and are taken once a day (two or three capsules)
• This compound can also be snorted, taken by mouth or used intravenously.
• It is frequently mixed with other psychosimulants
• With use, one can see: euphoria, excitement, improved mood and increased confidence.
• Adverse effects include: headache, dizziness, tremor, seizures, nausea, vomiting, dry mouth, dehydration, increased heart rate, decreased appetite, insomnia, anxiety, paranoia, and agitation.
Mephedrone is a cathinone derivative:

- The first synthesis was in 1929.
- Usually found in powder form or crystals
- Usually snorted or taken orally
- Can be mixed with water/wrapped in cigarette paper called “bombing”.
- Has also been reported to be used via rectal insertion, intramuscularly and intravenously
- The effects start in three-quarters to two hours if taken orally and can last two to four hours
- A “typical” mephedrone session lasts ten hours with a total dose of one gram over that period of time (usually split up and taken every two hours).
- Acute toxicity includes: heart rate greater than 140 beats per minute, hypertension, agitation, headaches and seizures. Death was reported in someone who combined this compound with heroin.

**Hallucinogens** - This class has many different compounds that can be used for this purpose. These include:

- Salvinorin A (Salvia divinorum)
- Lysergic Acid Amide
- Leunorine (Lion’s Ear)
- Tropane Alkaloids (atropine, scopolamine)
  - Datura stramonium
  - Atropa Belladonna
- Psilocybin
- Muscarine
- N,N-Dimethyltryptamine

**Salvinorin A:**

- Street names include: Magic Mint, Seer’s Sage, Lady SD, and Sally D.
- Used for centuries by the Mazatec shamans in Oaxaca Mexico for spiritual healing
- Used by chewing the fresh leaves, ingesting a tincture or juice from the leaf, or smoking dried leaves
- The psychoactive component is neoclerodane diterpene Salvinorin A.
- It is the most potent of all naturally occurring hallucinogens and is equal to LSD.
Unlike LSD which acts on the serotonin receptors, this works at the Kappa Opioid receptor as an agonist.

There is rapid onset when smoking (one minute) to ten minutes seen with buccal (oral) absorption.

It has a short half-life as the effect usually lasts 20 minutes.

Users state that they “enter another reality”, have improved mood, are calm, have increased insight and have a floating feeling. There are visual and auditory hallucinations that occur with use.

Adverse effects have included: sweats; mind racing; yawning; anxiety; irritability; insomnia; dizziness; fatigue; loss of coordination; and mental slowness.

Lysergic Acid Amide (LSA):

• ergot and fungi infected plants and produce
• ten times less potent than LSD
• Seeds are crushed and eaten or soaked in water or alcohol and eaten.
• The effects last four to eight hours and can include: auditory and visual hallucinations; elevated blood pressure and heart rate; memory loss; anxiety; panic attacks; acute psychosis; and suicidal thoughts.

An in-depth review of this material and the basis of this FYI can be found in “Legal Highs” - New Players in the Old Drama by Jolanta Zawilska in Current Drug Abuse Reviews, 2011, 4, 122 - 130.
Vivitrol Update

The use of naltrexone was first approved for the treatment of opiate dependence in 1984 and for alcohol dependence in 1994. In 2006, Vivitrol, a new formulation of this medication was approved for alcohol and in 2010 Vivitrol was approved for the prevention of relapse to opiate dependence. Naltrexone does not cause an antabuse-like aversion reaction. Naltrexone is an opiate receptor antagonist that blocks the pleasurable effects of alcohol and reduces cravings. Craving is defined as an intense desire and perceived need for some object/experience. Neurochemical alterations caused by chronic exposure to addictive agents form the biological basis of drug/alcohol cravings.

Oral naltrexone is effective in the treatment of alcohol and opiate dependence; however, a major limitation of its clinical utility is poor patient adherence to the daily dosing schedule. The solution; a biodegradable, long-acting naltrexone microsphere formulation was developed to achieve continuous naltrexone exposure for one month (Vivitrol).

Vivitrol (naltrexone for extended-release) is a formulation that uses microspheres that can be administered by intramuscular injection. It has received FDA approval for the treatment of alcohol dependence and opiate dependence. The dose of 380 mg is designed to be injected once every four weeks. Vivitrol is metabolized in the liver and is eliminated in the urine.

Vivitrol is a non-addictive and safe medication which uses pharmacologic means to improve the likelihood of successful treatment for alcohol and opiate dependence. Acknowledging that alcohol and opiate dependence are medical diseases with powerful physiological components points to an objective use of a medication to aid in the treatment of these diseases. While this medication may not be suitable for every patient suffering from alcohol and/or opiate dependence, it will aid the treatment provider in offering yet another alternative to complement ongoing support and treatment.

Several clinical studies have looked at the efficacy of Vivitrol:

Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. Garbutt JC; Kranzler HR; O’Malley SS; Gastfriend DR; Pettinati HM; Silverman BL; Loewy JW; Ehrich EW; JAMA. 2005; 293(13):1617-25

OBJECTIVE: To determine efficacy and tolerability of a long-acting intramuscular formulation of naltrexone for treatment of alcohol-dependent patients.

DESIGN, SETTING, AND PARTICIPANTS: A 6-month, randomized, double-blind, placebo-controlled trial conducted between February 2002 and September 2003 at 24 US public hospitals, private and Veterans Administration clinics, and tertiary care medical centers. Of the 899 individuals screened, 627 who were
diagnosed as being actively drinking alcohol-dependent adults were randomized to receive treatment and 624 received at least 1 injection.

**INTERVENTION:** An intramuscular injection of 380 mg of long-acting naltrexone (n = 205) or 190 mg of long-acting naltrexone (n = 210) or a matching volume of placebo (n = 209) each administered monthly and combined with 12 sessions of low-intensity psychosocial intervention.

**RESULTS:** Compared with placebo, 380 mg of long-acting naltrexone resulted in a 25 percent decrease in the event rate of heavy drinking days (P = .02) [corrected] and 190 mg of naltrexone resulted in a 17 percent decrease (P = .07). Sex and pretreatment abstinence each showed significant interaction with the medication group on treatment outcome, with men and those with lead-in abstinence both exhibiting greater treatment effects. Discontinuation due to adverse events occurred in 14.1 percent in the 380-mg and 6.7 percent in the 190-mg group and 6.7 percent in the placebo group. Overall, rate and time to treatment discontinuation were similar among treatment groups.

**CONCLUSIONS:** Long-acting naltrexone was well tolerated and resulted in reductions in heavy drinking among treatment-seeking alcohol-dependent patients during six months of therapy. These data indicate that long-acting naltrexone can be of benefit in the treatment of alcohol dependence.

In another study that can be found in *Lancet* (2011 Apr 30; 377(9776):1506-13). Krupitsk and his co-authors used Vivitrol in a double-blind, placebo-controlled, multicenter randomized trial. Their premise was that opioid dependence is associated with low rates of treatment-seeking, poor adherence to treatment, frequent relapse, and major societal consequences.

**DESIGN, SETTING, AND PARTICIPANTS:** They used a double-blind, placebo controlled, randomized, 24-week trial of patients with opioid dependence disorder. Patients aged 18 years or over who had 30 days or less of inpatient detoxification and seven days or more off all opioids were enrolled at 13 clinical sites in Russia. The patients were randomly assigned to either 380 mg XR-NTX (extended-release injectable naltrexone) or placebo. Participants also received 12 biweekly counseling sessions. Participants, investigators, staff, and the sponsor were masked to treatment allocation. The primary endpoint was the response profile for confirmed abstinence during weeks 5 - 24, assessed by urine drug tests and self report of non-use. Secondary endpoints were self-reported opioid-free days, opioid craving scores, number of days of retention, and relapse to physiological opioid dependence.

**RESULTS:** Between July 3, 2008, and Oct 5, 2009, 250 patients were randomly assigned to XR-NTX (n=126) or placebo (n=124). The median proportion of weeks of confirmed abstinence was 90.0 percent in the XR-NTX group compared with 35.0 percent in the placebo group. Patients in the XR-NTX group self-reported a median of 99.2 percent (range 89.1-99.4) opioid-free days compared
with 60.4 percent (46.2-94.0) for the placebo group (p=0.0004). The mean change in craving was -10.1 (95 percent CI -12.3 to -7.8) in the XR-NTX group compared with 0.7 (-3.1 to 4.4) in the placebo group (p<0.0001). Median retention was over 168 days in the XR-NTX group compared with 96 days (95 percent CI 63-165) in the placebo group (p=0.0042). Naloxone challenge confirmed relapse to physiological opioid dependence in 17 patients in the placebo group compared with one in the XR-NTX group (p<0.0001). XR-NTX was well tolerated. Two patients in each group discontinued owing to adverse events. No XR-NTX-treated patients died, overdosed, or discontinued owing to severe adverse events.

CONCLUSIONS: XR-NTX represents a new treatment option that is distinct from opioid agonist maintenance treatment. XR-NTX in conjunction with psychosocial treatment might improve acceptance of opioid dependence pharmacotherapy and provide a useful treatment option for many patients.

There was a comment on this article in the *Lancet* by Wolfe et al which did bring up some important points:

The *Lancet* study does not make clear what follow-up was done to evaluate post-treatment opioid overdose in the participants in the Russian trial.

The FDA’s Adverse Event Reporting System includes 51 reports of deaths associated with depot naltrexone between 2006 and 2010 (US Food and Drug Administration. Quarterly data from FDA Adverse Event Reporting System, 2006-10).

The FDA’s Adverse Event Reporting System includes 51 reports of deaths associated with depot naltrexone between 2006 and 2010 (US Food and Drug Administration - Quarterly Data from FDA Adverse Event Reporting System, 2006-10). Of these 51 reports, 19 were unique cases; only 1 was attributed by the reporting physician as possibly related to Vivitrol. During the time period of the FDA’s evaluation, approximately 45,000 patients were treated with Vivitrol. The FDA reviewed two studies of Vivitrol in opioid dependent patients in addition to the trial reported by Krupitsky et al. Since then, a retrospective, health-economic analysis addressed sample differences using instrumental variable analysis on demographic, clinical, utilization and provider characteristics (Baser et al. 2011). Results primarily showed comparable or lower total healthcare costs for patients treated with XR-NTX (N=156) vs. agonists, apparently because mean days of refill persistence did not differ significantly among patients treated with antagonists vs. agonists (XR-NTX 61.49 days; buprenorphine 68.92 days; methadone 62.8 days - and XR-NTX patients experienced fewer hospitalizations: XR-NTX patients had 93 opioid-related hospitalizations per 1000 patients over 6 months, vs. 249 for buprenorphine (p=0.007) and 198 for methadone (p=0.025). Importantly, these differences were measured during a period that included, on average, several months after the pharmacotherapy treatment ended. (Baser O,

Experience with oral naltrexone highlights the importance of adequate investigation of overdose risk following treatment with depot naltrexone. Risk of overdose for detoxified heroin-dependent patients receiving oral naltrexone treatment is well documented. A review of 13 trials of Pharmacotherapies for opioid dependence in Australia showed that the heroin overdose rates were more than trebled (at 6.8 per 100 person-years) for patients on oral naltrexone treatment compared with those receiving opioid agonist treatment (1.9 per 100 person-years) (Digiusto E, Shakeshaft A, Ritter A, O’Brien S, Mattick RP. Serious adverse events in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD). *Addiction* 2004; 99: 450-60.)

**What patients cannot take Vivitrol?**

- Taking opioid medications (must be off all opioids for a minimum of 7 - 10 days)
- In opioid withdrawal or dependent on opioids
- Any individual who is allergic to naltrexone, carboxymethylcellulose, polysorbate or polyactide-co-glycolide (PLG)
- Have acute or severe liver or kidney disease
- Have a positive urine drug screen for opiates
- Fail a Naloxone challenge test (see Physician’s Desk Reference)
- Pregnant women or nursing mothers.
- This medication has not been studied in the geriatric or pediatric population.
- This medication has not been studied in those younger than 18 years of age.

**What are the possible side effects when using Vivitrol?**

- Nausea
- Difficulty sleeping
- Anxiety
- Abdominal cramps
- Diarrhea
- Joint and muscle pains
- Headaches
- Injection site pain, nodules, and severe injection site reactions

Mild nausea is the most common side effect following an *initial* Vivitrol dose. It is usually not associated with anorexia or vomiting, and is typically limited to two to three days post-injection. It tends to occur following the first injection, when blood levels of
naltrexone rise quickly, but tends not to re-occur upon subsequent injections, when naltrexone is already at a steady-state. Rates of nausea and GI symptoms are lower when using Vivitrol compared to oral naltrexone.

Soreness at the injection site is common and can be managed with massage, NSAIDS, or ice packs. This is a similar side effect to other IM buttocks injections, such as antibiotics, and is not related to naltrexone itself. Non-painful nodules lasting several weeks post-injection are common, self-limited, and not concerning; they resolve steadily over four to six weeks.

Severe injection site reactions have been reported in several cases since Vivitrol’s alcohol approval in 2006 and likely stem from mis-injection into subcutaneous adipose tissue rather than muscle. Obese persons and those with increased hip and buttock adipose tissue are likely at greater risk. Providers should use their judgment and only inject Vivitrol when they are confident an IM injection can be delivered successfully. Severe injection site reactions are similar to sterile abscesses and should be treated with a prompt referral to an appropriate medical provider such as a general surgeon. While severe injection site reactions are rare, this risk prompted several FDA alerts from December, 2009 to early 2010.

Fishman reported a case of precipitated withdrawal in a 17-year-old adolescent female receiving Vivitrol for opioid dependence, following her third serial monthly dose of the medication, several days after using Oxycodeone with mild intoxication. The author’s conclusion was that, in some circumstances, the opioid blockade may be overcome when naltrexone levels drop towards the end of the dosing interval, producing vulnerability to subsequent naltrexone-induced withdrawal. This may provide cautionary guidance for clinical management and dosing strategies. (Fishman, M. *Addiction*, 103, 1399-1401)

All patients considering Vivitrol treatment should be counseled regarding these potential side effects.

In younger opioid dependent patients (N=133), also in a community setting, Fishman et al (2011) reported retention and relapse in a chart review study. Patients who received treatment without anti-relapse pharmacotherapy had mean cumulative retention of 10.3 weeks vs. 16.3 weeks with XR-NTX (p=0.0001) and 15.9 weeks with buprenorphine (p=0.0008). Mean cumulative time without opioid use (combining self-report and urine testing) was 7.0 weeks for those on no medication vs. 13.7 weeks with XR-NTX (p<0.0001) and 10.6 weeks with buprenorphine (p=0.009). (Fishman M, Curran E, Shah S, Perry-Parrish C. Treatment outcomes with relapse prevention medications for opioid dependence in youth. Presented at the 73rd Annual Meeting of the College on Problems of Drug Dependence, Hollywood FL, June 22, 2011).
**Special Populations**

In the emergency pain management situation, it is suggested that the patient who had been receiving Vivitrol be managed with regional analgesia, conscious sedation, non-opioid pain medications or general anesthesia.

The patients should be monitored for the development of depression or suicidal thoughts. In the patient who is drinking, Vivitrol will not decrease the withdrawal symptoms.

The opiate dependent patient who stops Vivitrol should be monitored and educated about the risk of opiate overdose.

**Who is a candidate for Vivitrol?**

A patient with an alcohol-dependence and/or opioid 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 not have signs of significant liver or kidney disease.

Vivitrol is appropriate for any opioid-dependent client who can achieve abstinence long enough for naltrexone induction. Abstinence in the opioid-dependent person is best achieved with a detoxification protocol that allows for the complete elimination of opioids from the patient’s system over a prescribed number of days (depending on the half-life of the opiate/opioid.) Non-opioid-based detox protocol, such as one using clonidine, is currently the most efficient way of achieving this. See Ockert et al., Journal of Addiction Medicine, Volume 5, Number 2, June 2011.

**Counseling**

Counseling of the opioid-dependent patient should begin from the first contact, well before the detoxification begins, through the entire post-detoxification/Vivitrol initiation and stabilization periods. This is an opportunity to explore with the patient any issues or concerns they may have with utilizing a medication to support their recovery and to develop the understanding that their ongoing work in counseling can help them resolve the challenges ahead. It is also the opportunity to strengthen a therapeutic alliance and explore with them how you are prepared to respond to critical events they may face.

At the initial counseling, Vivitrol must be thoroughly explained:

- The nature of the opioid antagonist
- How it differs from agonist treatments
- The benefits of using the antagonist approach, including the rapid up-regulation of the mu-ligand receptor system with Vivitrol: the concept of neuro-biological recovery.
• Naltrexone/Vivitrol eliminates some of the most severe protracted-abstinence symptoms, especially lack of energy and depression
• Faster restoring of endorphin activity
• Unlike agonist therapy, Vivitrol is unlikely to reduce sexual drive.
• The convenience of monthly administration.
• Reduced cravings and protection from impulsive relapse.
• Greater ease of establishing non-drug-related life patterns: less contact with drug-involved persons.
• If naltrexone is taken with opioids/opiates remaining in the nervous system it will cause precipitated withdrawal.
• Vulnerability to overdose following discontinuation of opioid antagonists (Vivitrol, Naltrexone) can increase due to lack of tolerance.

Follow-up visits should encourage the patient to express not only their physical response to the medication, but also the emotional adjustments they may have made in accepting this form of treatment. It’s possible patients may see themselves as cured and ready to move on, or tethered to a crutch due to some perceived inadequacy on their part; either of which might lead to a precipitous discontinuation of treatment. It is important that the patient perceive that the practitioner is interested and understanding of their perceptions and prepared to help work them through.

*Following discontinuation of Vivitrol, patients should be given the option to continue on oral naltrexone.*
Botulism Cases blamed on Black Tar Heroin

Two people have been hospitalized in the Seattle area with suspected cases of botulism probably contracted by injecting black tar heroin.
Four additional cases have been reported in Texas over the last few weeks.

Black tar heroin, produced in Latin America and sold mainly in Western U.S. states, is a cruder, less-refined form of heroin that contains more morphine derivatives than pure heroin.

Botulism Advisory (Seattle Dept of Health)

Epidemiology

- Botulism is a neuroparalytic disease caused by botulinum toxin.
- Spores are present in soil and may be found on agricultural products.
- Exposure to preformed toxin may occur through ingestion, inhalation, or breaks in the skin.
- Infant botulism is the most common form.
  - About 100 cases are reported annually to CDC.
  - Most of the time, the source is unknown.
  - Honey can be a source of botulism and should not be fed to infants.
- Toxins formed when foods are inadequately heated during canning can cause food-borne botulism.
  - Poorly prepared, home canned vegetables ("low-acid" vegetables such as beans, carrots, peppers, and corn) and fruits are the most common source.
  - The incubation period is 12 to 72 hours.
- Contamination of devitalized tissue causes wound botulism (rare).
  - May be a complication of injection drug use (particularly black tar heroin) or injury.
  - The incubation period is four to 14 days.

Microbiology and Pathogenesis

- *Clostridium botulinum* is a gram-positive, spore-forming, anaerobic bacillus.
- Vegetative cells germinate from spores under anaerobic conditions and produce botulinum toxins.
- Toxins can be inactivated by heating (>85°C for five minutes).
• Spores are very resistant to harsh environments and may survive boiling for up to three to four hours.
• Toxins are inactivated in fresh water within three to six days, and inactivated within 20 minutes by standard potable water treatment (e.g., chlorination and aeration).
• Botulinum toxins act by irreversibly binding to the neuromuscular junction, preventing the release of acetylcholine and muscle contraction.
• Seven antigenically distinct toxin types (A, B, C, D, E, F, G) exist; the majority of naturally occurring disease in humans is caused by types A, B, and E.

Botulism and Bioterrorism

• Aerosolization of toxin and sabotage of the food supply are thought to be the most likely modes of dissemination of botulinum toxin in a biological attack.
  o Gastrointestinal symptoms are thought to result from other bacterial metabolites in food and thus may not be present if a purified form of the toxin is used.
• Inhaling aerosolized spores would produce inhalational botulism - a form that does not occur naturally; the incubation period is likely to be less than that for food-borne illness.

Clinical Presentation

• The classic syndrome is characterized by:
  o acute, descending, symmetrical paralysis with prominent bulbar palsies. afebrile patient.
  o clear sensorium (i.e., normal mental status; toxin does not cross the blood-brain barrier).
  o normal sensation (with the exception of paresthesias secondary to anxiety).
• Disease typically begins with cranial nerve dysfunction, progressing to proximal muscle weakness.
• Prominent neurologic findings in all forms of botulism include ptosis, diplopia, blurred vision, enlarged or sluggishly reactive pupils, dysarthria, xerostomia, dysphonia, dysphagia, and dystonia.
• In severe cases, complete flaccid paralysis involving pharyngeal or respiratory muscles develops, requiring ventilatory support.
• Abdominal cramps, nausea, vomiting, or diarrhea may accompany the food-borne form.
• In infants, illness may begin with constipation and poor feeding, followed by neuromuscular paralysis, hypotonia, or weakness within two hours to eight days after exposure.
**Infection Control**

- Botulism is not spread person-to-person; standard precautions are adequate.

**Diagnosis**

- Differential diagnosis includes Guillain-Barre syndrome, tick paralysis, myasthenia gravis, Lambert-Eaton syndrome, stroke or CNS mass, paralytic shellfish poisoning, poliomyelitis, aminoglycoside and belladonna toxicity.
- Electromyogram (EMG) findings are non-specific but may be helpful in differentiating from other causes of flaccid paralysis.
- Diagnosis is confirmed by mouse bioassay, available through public health labs for reported suspect cases.
- Serum, wound exudate or tissue, stool, and gastric secretions are appropriate specimens for laboratory testing.
- For suspected food-borne illness cases, samples of the suspected food should also be obtained for testing.
- Contact Public Health - Seattle & King County for assistance with submission of specimens for botulism testing.

**Treatment**

- Ventilatory assistance and other supportive care is the mainstay of treatment.
- In wound botulism, the wound should be surgically debrided and antibiotics administered.
- Aminoglycosides and clindamycin exacerbate the neuromuscular blockade and are contraindicated.
- Recovery depends on regeneration of new motor axons and may take weeks to months.
- Botulism antitoxin is most effective if given early in the clinical course. Antitoxin will not reverse existing paralysis, but will prevent additional nerve damage if given before all circulating toxin is bound to the neuromuscular junction.
  - Types A, B, and E antitoxin are available from CDC via local and state health departments.
  - Antitoxin should be requested from Public Health as soon as botulism is suspected.
  - Antitoxin should be given as early as possible, and is most effective if given within 24 hours of symptom onset.
  - Screening for hypersensitivity is necessary prior to administration.
For treatment of infant botulism caused, human-derived botulism antitoxin is available through the California Department of Health Services (510) 231-7600.

**Prevention and Prophylaxis**

Preventive measures for avoiding exposure to botulinum toxin include following proper home canning techniques and avoiding food from damaged cans (i.e., slits, holes, dents or bulges).
Driving While Impaired

An article in the *Journal of Studies on Alcohol and Drugs* by Romano and Voas (July 2011) looks at the fatally injured drivers in states reporting into FARS (Fatality Analysis Reporting System) where toxicology tests were performed.

- Of the 44,239 reported fatally injured drivers, 25 percent had a confirmed positive test for drugs.
  - 23 percent were positive for cannabis
  - 23 percent were positive for stimulants

The article looks at four different types of events found in the fatally injured:

- Speeding
- Failure to obey/yield
- Inattention
- Seatbelt nonuse

It was found that drug use increased risk of crash through influence on driving skills at the time of the crash. It was also suggested that drug users could exhibit an increase in risk-taking or impulsivity.

Some drug specific findings include:

- Cannabis use was associated with speeding and seatbelt nonuse
  - If a crash was the result of speeding, cannabis was seen in 26.8 percent of the fatalities
- Stimulant users showed an increase in failure to obey/yield and speeding. The failure to obey/yield was similar to that seen in alcohol users
  - If a crash was the result of speeding, stimulants were seen in 25.5 percent
- In multidrug users, 60 percent consumed stimulants and 35 percent had stimulants and cannabis
- Miscellaneous and over the counter class was found to be protective in the four crash types. The theory is that the users take these as medications, thus are lower risk takers who tend to drive more carefully.
- Besides drug use, speeding was also associated with a BAC of greater or equal to 0.08, age of 34 or younger and male gender.

Romano and Voas found that alcohol involved fatal crashes showed that where the driver was impaired, it is the alcohol that was the main source of impairment. Other drug use was less important, or at least it was not noted to be a synergistic effect.
Phillips and Brewer in the Research Report found in *Addiction* (June 2011) looked at the relationship between serious injury/fatality and blood alcohol concentrations. They note that blood alcohol content at levels as low as 0.03 percent significantly impaired cognitive functions which rely on perception and processing of visual information. They also state that it is widely acknowledged that a high BAC is the leading risk factor in automobile accidents. However, there is disagreement as to what constitutes a dangerously high BAC (Sweden 0.02 percent, Japan 0.03 percent, Germany 0.05 percent and US 0.08 percent).

They report that three mechanisms mediate between “buzzed driving (levels lower than 0.08 percent) and high accident severity as compared to sober drivers. Those with levels less than 0.08 percent are significantly more likely to speed, to be improperly seat belted and to drive the striking vehicle. In addition, there is a strong dose - response relationship for all three factors in relation to accident severity. The greater the BAC, the greater the average speed of the driver and the greater the severity of the accident.
Our conclusion is that continual education is necessary in regards to the affects of drinking and driving.
Tampering with Prescription Opioids

Tampering is used by prescription drug misusers to provide a high blood concentration of the medication in a short period of time so as to produce a potent and rapid “high”.

- Oral opioids can be taken in an “above recommended dosing” using the normal route of administration.
- Oral opioids that are extended release can be taken intact (most widely used route) or they can be crushed and/or dissolved, which disables the extended release mechanism, thereby accelerating the release of the opioid by either ingestion, injection, snorting or smoking.
- Transdermal and solid oral prescription opioid (PO) formulations can be abused by ingesting (with or without tampering), snorting, or injection (both requiring tampering). The problem has increased over the last decade.
- Tampering varies greatly by product; immediate release medications don’t need to be tampered with to induce a high.
- Tampering is relatively common although only a small number of studies have examined this issue. While most misusers swallow the oral medication intact, the most frequent form of tampering is chewing the medication before swallowing. Upwards of 60 percent of college students who misuse medications chewed it before swallowing - Researched Abuse, Diversion and Addiction - Related Surveillance System (RADARS).

The most prevalent route of administration for nonmedical use is ingestion, followed by snorting and injection. Smoking appears to be the least common method of misuse of prescription opioids. The prevalence also differs by population. McCabe et al showed that in college students, oral (97 percent) and intranasal (13 percent) were the leading routes. While Davis and Johnson in 2008 showed that among street drug users in New York City, 66 percent ingest, 15 percent snort and 4 percent inject. It appears that over the last decade or more, injection as a route has decreased. This is thought to be due to HIV and other infectious diseases prevention efforts.

The route of administration also tends to differ by opioid product. Extended release Oxycodone (brand names: Dazidox, OxyContin, Oxyfast, OxylR, Percolone, Roxicodone, Roxicodone Intensol, M-Oxy, ETH-Oxydose, Endocodone) is misused by snorting as seen in most studies 57-92 percent; though it is ingested 27-89 percent and injected 23-59 percent, again depending on the study and the group studied.

- Hydrocodone plus acetaminophen (Vicodin, Lortab) is mostly abused by ingestion, followed by the intranasal route. Injection is rare.
- Morphine sulfate products are most misused by injection (up to 40 percent).
- Hydromorphone is commonly injected (90 percent).
- Fentanyl is ingested (55 percent), injected (32 percent) and smoked (19 percent). It is the only medication that is substantially abused by smoking (19 percent).
Buprenorphine in Europe is injected 48 percent of the time. While in Australia it is injected 10 percent of the time and in the United States injecting is very rare. Methadone is ingested 72 percent and inhaled 10 percent. Injection can be seen in 8-11 percent of misusers.

As expected, there is progression from ingestion in the inexperienced user to snorting and/or injection as they become more experienced. The oral route is the most popular in all age groups, however, those under 30 years of age had a higher tendency to inject and snort as compared to those greater than 30.

There are significant health consequences to misuse and tampering. Life threatening events occur in 7.8 percent of misusers and death occurred in 1.1 percent. Injecting was associated with the highest rate of death. The four products that caused the most deaths (all routes) were methadone, fentanyl, hydrocodone and oxycodone. Other significant negative medical consequences that have occurred are:

- Nasal and patatal necrosis and perforation
- Hypersensitivity reactions
- Skin infections
- Systemic infections
- Viral infections - Hepatitis A, B and C, HIV
- Fungal endocarditis and ophthalmitis

Tamper resistant formulations take into account the data and thus ingestion is looked at as a primary prevention area, though formulations have been developed to also inhibit crushing, snorting and injecting.

*For a more complete review - Katz, Dart et al in Am Journal of Drug and Alcohol Abuse 2011