Designer Drugs: Medical Aspects and Clinical Management

Mark W. Stanford, PhD

INTRODUCTION

During the past several years there has been a growing concern over the increasing problem of synthetic street drugs known as "designer drugs." California State Senator John Seymour, during hearings of the Senate Select Committee on Drug Abuse, called the designer drug problem potentially enormous.

Clinicians and chemical treatment agencies have identified some very severe neuro-toxic consequences in heroin patients who have injected a synthetic form of meperidine (Demerol) (Drug induced Parkinsonism, Langston et al.). Because of the relative ease in which "kitchen chemists" can synthesize a variety of compounds, along with the cost effectiveness of such procedures, we can reasonably infer that we are seeing just the "tip of the iceberg" in terms of a major health concern with new problem aspects for the chemical dependency treatment field.

Because of this new dimension in chemical abuse patterns, practitioners and health agencies alike are in need of more information. We already know of several chemical analogs (chemical variations from a parent compound) which are circulating within the chemically dependent and chemical using population. These include analogs of fentanyl, meperidine, phencyclidine (PCP), and MDA/

Mark W. Stanford is Director of Clinical Services, Pathway Society, Inc., 1659 Scott Boulevard, #30, Santa Clara, CA 95050.

Alcoholism Treatment Quarterly, Vol. 4(4), Winter 1987

MDMA. The problem exists in that even through a minute chemical alteration is made during the synthesis process, severe medical consequences can and have occurred to the individual user. We need to know more about what is going on in the areas of kinetics, pharmacology, toxicity, distribution of the new compound, and how treatment might be effected.

The term, "designer drugs," was originally coined to mean the ease with which underground "chemists" could manufacture a psychoactive compound designed to meet the consumer's wishes. This means that duration of effect, quality of effect, and CNS effects could be chemically manipulated in the "lab" to meet the desires of the customer. However, the term has taken on a much broader meaning. As the manufacturing of chemical compounds becomes more and more prevalent, designer drugs have less to do with a user's request and specifications for a tailor-made high. These synthetics are being made quickly and rushed out to the streets without anyone knowing the extent of their toxicity. Controlled Substances Analogs, a realistic name for the designers, are any illegally manufactured psychoactives in clandestine labs throughout the nation.

At the top of the medical concerns list a synthetic compounds are the inherent and inevitable hazards of chemical design, manufacturing, and distribution. Because no one can attest to the "kitchen chemist's" knowledge of chemical synthesis, we do not know the product's potency, purity, or toxic potentiation for cellular damage. In essence, there are no quality control measures on the street for the many clandestine labs brewing up synthetic compounds.

Some of the inherent dangers of Controlled Substances Analogs are:

- Knowledge of the chemist for synthesizing compounds ????
- Potency or drug strength of compound ????
- Impurities/Contaminants of compound ????
- Distribution area/Epidemiology ????
- Cleanliness of labs (open to bacterial/viral agents) ????

Researchers in the field do not expect this situation to simply go away. Neither do they feel this situation to be just a fad or trend running a limited course. When you ponder the implications in-

volved in designer drug manufacturing, one can begin to see why. The "cooker" (kitchen chemist) can synthesize a compound for an inexpensive initial cash output. The finished product, because of marketing and consumer demand, yields a very high profit margin. It has been noted, for example, that for a $500 investment for the basic compounds needed to produce PCP, a profit margin in excess of 600% can be realized. The monetary incentive is there! Also, the cooker does not have to deal with the legal issues surrounding importation. He or she does not have to risk the harsh penalties of getting caught trying to smuggle drugs into the country. In addition, because there is potential for thousands of analogs and because the Drug Enforcement Agency (DEA) cannot restrict a compound it doesn't know about, often the cooker is synthesizing a compound that is actually legal (unknown to the DEA) and, therefore, not on any schedule for restriction. Because of these factors, we can make a reasonable inference that the situation will not improve or go away.

Since a multitude of synthetic variations for different compounds are possible, and because we only know of a few in comparison, the clinician of the 1980s must become aware of the enormous problems that this situation presents. Indeed the objective for this presentation is to begin the process of understanding.

Practitioners in the field of chemical dependency would do well to be versed in the clinical manifestations and subsequent treatment directions to take when they encounter a patient with a history of synthetic drug use. Too many times a patient goes unnoticed or is excluded from a treatment program only because the symptoms are unfamiliar to the treatment staff. We cannot simply sit back and wait for the media, the federal government or the state to tell us about a new compound. Nor can we ignore the situation and hope that an analog neurotoxin does not come to our clinic's area. We cannot minimize the problem because it is new and we have "never seen or treated anything like this before, therefore, it must not really exist."

There is a need for networking together and, individually, to watch closely for new clinical signs and symptoms in our patients and to pass the word on to our colleagues when we become aware or suspicious of a new compound or analog occurrence. Finally, and

in everyone's best interest, we must engage in rigorous research to stay on top of developing trends in the synthetic marketplace and to provide subsequent predictions concerning the various kinds of presenting problems that might be anticipated in the treatment setting.

This presentation only begins the process. The focus of this presentation will be on the analogs and synthetic compounds of fentanyl, meperidine, phencyclidine, and MDA/MDMA. Each section will have subsections in the areas of:

1. Classification
2. Kinetics
3. CNS effects
4. Patterns of use
5. Some treatment suggestions

The chemicals focused on in this presentation are not the only designer drug compounds. However, I felt these to be of greatest concern based on epidemiologic findings on prevalence of synthetic compounds most abused as of 1986. The information is certainly not exhaustive. It does however, provide for a framework of understanding which can serve as an impetus for clinicians to delve even deeper into the various aspects of chemical dependency treatment.

FENTANYL AND MEPERIDINE (DEMEROL)

Classification

Synthetic Narcotics. Medicinal use of the fentanyls is for anesthetic purposes and meperidines are painkillers. Some of the fentanyl analogs are thousands of times more potent than heroin or morphine. There are six known fentanyl analogs on the street:

- Alpha-methyl fentanyl
- Para-flouro fentanyl
- Alpha-methyl acetylfentanyl
- Benzyl fentanyl (non-narcotic)
- Fentanyl
- 3-methyl fentanyl

Street names for these illicit analogs include: China White, Persian White, synthetic Heroin, New Heroin, Fentanyl and new synthetic Heroin.

The fentanyls, although not structurally the same, are pharmacologically the same as other narcotics and as such possess the same kinetics and clinical side effects as do their narcotic cousins. Problems may be encountered because of unknown potency levels and impurities.

Meperidine analogs include (see Figure 1):

- MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine)
- PEPAOP (1-(2-phenylethyl)-4-phenylacetoxypiperidine)
- PEPTP (1-(2-phenylethyl)-4-phenyl-1,2,3,6-tetrahydropyridine)

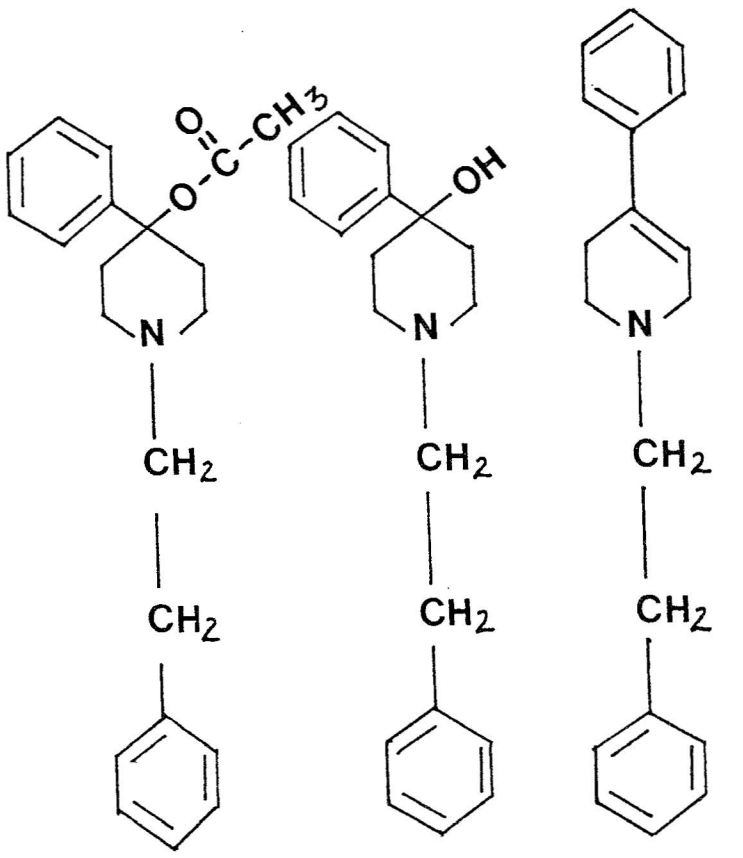
The MPTP analog is the compound associated with drug induced Parkinson's disease. MPTP is a neuro-toxic contaminant that commonly occurs during the synthesis of MPPP.

To date, there is uncertainty as to the toxic symptomology of the other meperidine analogs. However, we know that the PEPAOP compound contains the 4-5 double bond that has been associated with the striatal nigras toxic consequences of MPTP.

Kinetics

Fentanyl is a very lipid soluble compound and is thus distributed from the blood to the parenchymatous tissues quickly, allowing for a fast onset of action. Absorption and distribution are quick acting as well as is elimination. The compound is first distributed to bodily tissues. The liver metabolizes the compound and excretes the metabolite which in turn allows for a redistribution of the drug. As drug plasma levels drop, the fentanyl compound is released back into the blood from the body tissues where it again becomes metabolized and eliminated. The chemical engineering of the fentanyls has designed the structure to provide for a long lasting analgesic effect.

We know that the kinetic properties of meperidine (Demerol) are similar to those of other synthetic derivatives of morphine. However, the exact nature of the mechanisms of action for the analogs is



PEPAOP **PEP-** piperidinol **PEPTP** analog of mptp

meperidine analogs
and an mptp analog in itself

FIGURE 1

not clear. Opioids are readily absorbed from the gastrointestinal tract, nasa mucosa, and lung (swallowed, snorted, or smoked) but the parenteral route of administration is utilized most. Metabolism is largely conjugated by the liver like other opiate compounds. Thus a significant amount is excreted or eliminated. Although only a small amount of the drug is seen to cross the blood brain barrier, two analogs with neuro-toxic properties have caused severe and specific neurologic damage (MPTP, PEPAOP). The meperidine analog neurotoxin, MPTP, is a simple molecule consisting of pyridine structure with single phenyl and methyl groups attached (see Figure 2).

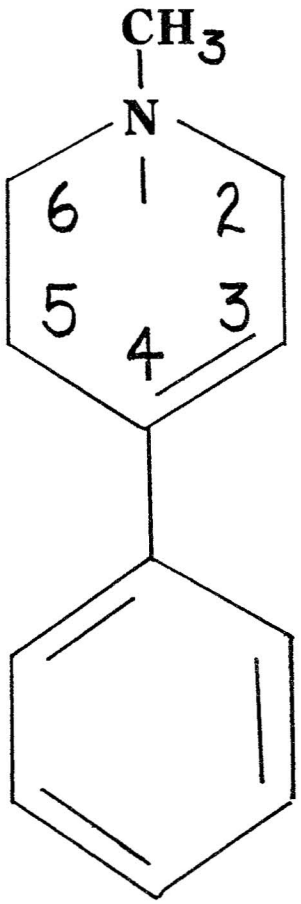
CNS Effects

Although the fentanyls and the meperidine analogs contain the usual opiate analgesic properties (analgesia, drowsiness, mental clouding, and changes in mood), there are some important and unique medical concerns as to their effects on the central nervous system. Because of some of the fentanyl derivatives' high potency, overdose is a definite concern. Complications include: pulmonary edema and congestion, direct depression of the mid-brain respiratory center, generalized anaphylactoid reaction to opioid adulterants and/or impurities, and direct cardio-toxic effects. Analogs of abuse, like all other narcotics, produce a tolerance and a physiologic dependence.

Perhaps the single most known concern for the meperidine analogs is the drug induced Parkinsonism that is correlated with MPTP. This analog is very selective in its neuro-toxic effect as it causes a degeneration in the dopaminergic system of the zona compacta within the striatal nigras system of the mid-brain (Langston et al.). It is important to note that the MPTP compound is a classic neurotoxin and not just a simple pharmacologic agent.

Patterns of Abuse

Both the fentanyls and the meperidine analogs have been utilized by the street user for sometime now. As early as 1979 illegal synthesis of the fentanyls began and were marketed under the name of "China White." Several of the derivatives have a potency exceed-



MPTP

neuro-toxin mptp
synthetic meperidine analog

FIGURE 2

ing 7000 times that of morphine. As such, and since there is no quality control for the street chemist, these compounds are potentially fatal. Dr. Will Spiegelman of Stanford University Hospital said, "It can take years to become addicted to alcohol, months to cocaine, and one shot for fentanyl." Typically, an addict will inject a similar amount of high potency fentanyl to a usual dose of heroin and unknowingly overdose. Well over 100 deaths have occurred due to fentanyl overdose recently, according to the medical research in Santa Clara County, California.

During the time period between 1981 and 1982 the MPPP neurotoxic contaminant MPTP was created and put out on the streets as "new heroin." This is the meperidine analog that produced the Parkinson's disease in its users. Research done by IMR states that over 400 addicts in the San Francisco Bay Area have been identified with having developed the disease. These analogs can be inhaled or injected with more prevalent use of the later.

Treatment Suggestions

The fentanyls are pharmacologically like other narcotics and therefore will produce all the clinical adverse reactions, side effects, and toxic behaviors. Narcotic antagonists will thus work effectively in terms of reversing the effects of the synthetic narcotic.

It is important to note that in all areas of addiction, the treatment of choice is introducing the patient to the self-help program of Narcotics Anonymous (NA) and Alcoholics Anonymous (AA). This will enable the person to learn about and apply a set of principles that will carry him or her through a lifetime of self-awareness, self-development and emotional stability in a drug free manner. During the acute phase of treatment regime where drugs are indicated for lifesaving measures, it should be emphasized that this procedure should be discontinued as soon as the patient is stable (where there is the absence of chronic medical conditions). Treating the disease of addiction with chemicals is ironic and not in the best interest of the patient.

In addition to the introduction of the patient to the 12 step program of NA/AA, it is important for the clinician to be able to identify and assess the patient who may have been exposed to the fen-

tanyl or meperidine analogs. Identification/assessment procedures will be addressed later.

Treatment measures would also include an educational component. There is a lot of misinformation about the synthetic compounds of the streets and oftentimes the addict is either underinformed or misinformed about the chemical (i.e., China White implies high grade heroin from Asia when actually it is a very potent analog). The educational component to the treatment should include a discussion on the lack of quality control for the "cookers," potency and overdose statistics, toxicology and impurities print issues, and other drug awareness information. The clinician needs also to be aware of the possibility of the addict's uncanny ways of rationalizing facts and figures and that there may be a hidden glamour in the patient's mind about "walking on the edge" while using an analog.

Regarding the meperidine analogs, careful consideration must be paid to observation, interviewing, and networking with other agencies. Epidemiologic statistics from the Centers for Disease Control (CDC) have shown us that the MPTP analog appeared on the streets during the 1981-1982 period. However, we do not know the full extent of its circulation/distribution and just because we have not seen a flurry of afflicted addicts does not mean the crisis is over. The Centers for Disease Control in Atlanta, Georgia conducted a study to define the extent of the problem of meperidine analog exposure to addicts in California. This study was done during 1984 to obtain some formalized numbers of people effected by the neurotoxic MPTP. They defined a set of symptoms to watch for as well as directions to take in the event a positive observation is made (see Figure 3).

MPTP acts as a toxin in that it selectively causes cellular degeneration within the zona compacta of the substantia nigris, a group of cells responsible for the initiation of muscle movement. The extent of neurologic damage can be varied from one patient to the next as it is related to the strength of the analog, the length of repeated usage, and the period of time that has elapsed before treatment was started. It must be emphasized that the exact number of current meperidine analogs is unknown. Therefore, we do not know how many other potential neuro-toxic analogs exist. We could even con-

ACUTE AFFECTS OF MEPERIDINE ANALOG EXPOSURE

SEVERE BURNING IN VEIN

METALLIC OR MEDICINE - LIKE TASTE IN MOUTH

JERKING OF LIMBS

TIGHTNESS, STIFFNESS, ACHING OR FREEZING OF MUSCLES

PROBLEMS WITH BALANCE AND COORDINATION

NUMBNESS OF EXTREMITIES

LOSS OF FACIAL EXPRESSION

INCREASE OF OILINESS OF SKIN

DIFFICULTY OPENING EYES

BLURRED VISION

SHAKING OR TREMORS

BRADYKINESIA

DIFFICULTY IN SPEAKING

DIFFICULTY IN SWALLOWING

DROOLING

HALLUCINATIONS

PROFUSE DIAPHORESIS

FIGURE 3

ceivably see a comeback of MPTP or one of its own analogs. So, it is important to be familiar with the symptomology of the MPTP compound.

Dr. Gary Henderson, a pharmacologist from the University of California at Davis, believes that the chemist who synthesized meperidine (and who inadvertently got the MPTP by-product), is a very intelligent person who knows chemical synthesis. It is highly

conceivable that this person predicted the sequence of legal events for restricting new compounds and went ahead and developed several new compounds some time ago. All he would need to do then is to just sit back, wait until one of the analogs became recognized and restricted, and then release one of the other new compounds. This means that for clinical personnel in the field, we need to be constantly on the alert for signs and symptoms of patients. We cannot get into a comfortable practice of treating the "same old hype."

Dr. J. William Langston, of the Institute for Medical Research and Valley Medical Center of San Jose, California, has defined some progressive symptoms of heroin users who have been exposed and effected by the MPTP analog (see Figure 4).

If you notice any of these symptoms in a heroin patient, or other atypical patterns of withdrawal syndrome during the interview ask the patient about his or her history of use. Dr. Langston has outlined criteria for MPTP exposure that should be utilized during assessment. Should your patient be a definite exposed person, or should you feel that your clinical assessment suspects exposure, it is recommended that you refer the patient to a neurologist for a full workup. Additionally, it would be in the patient's best interest to have the case reported to either CDC (Centers for Disease Control) and/or the Institute for Medical Research for specialized follow-up. These contact addresses are in the references section. *LEVO-DOPA* is the treatment of choice for these patients. Research is finding some positive results from the administration of Deprenyl. It is an MAO-B type inhibitor and as such may inhibit neuro-toxic development. Yet any conclusive remarks about whether deprenyl will prevent disease progression would be premature.

We can only use good clinical observation and judgment along with the patient's subjective response to the symptoms questionnaire to assess the likelihood of MPTP exposure. However, evidence from a Positron Emission Tomography (PET) and measures of dopamine metabolites from spinal fluid will probably be the most optimum method to gather objective data on MPTP neuro-toxic exposure and clinical criteria. This procedure might be implemented as a result of an initial assessment should findings be positive.

At this point in time, the medical treatment of choice for patients exposed to MPTP is the administration of Levo-Dopa, a sympto-

CRITERIA FOR ASSESSING MEPERIDINE ANALOG EXPOSURE

I PATIENT EXPERIENCED ALL OF THE FOLLOWING:

A) BURNING AT INJECTION SITE
B) USED THE COMPOUND BETWEEN THE PERIOD OF JANUARY - AUGUST 1982
C) DRUG WAS OBTAINED IN APPROPRIATE PLACE WHERE MPTP WAS VERIFIED: (IN CALIFORNIA INCLUDES KING CITY, GREENFIELD, SOLEDAD, WATSONVILLE, HAYWARD, SAN JOSE).

II THREE OR MORE OF THE FOLLOWING DURING THE ACUTE PHASE OF INTOXICATION:

A) SOURCE WAS A KNOWN DEALER OF MPTP
B) UNUSUAL HIGH (DIFFERENT FROM THE TYPICAL ANALGESIC EFFECT)
C) TREMOR
D) FREEZING UP
E) DROOLING
F) SLOWED MOVEMENT (HIGHLY REPORTED PROGRESSIVE SYMPTOM)
G) OILY SKIN
H) RIGIDITY OR STIFFNESS (MOST REPORTED PROGRESSIVE SYMPTOM)
I) JERKING OF EXTREMITIES (WHEN AWAKE)
J) VISUAL CHANGES

FIGURE 4

matic treatment direction that is the same for idiopathic Parkinsonism.[1] However, new studies are showing that the MPTP compound is converted to a toxic derivative MPP+ by monoamine oxidase B enzyme in the brian (see Figure 5). The toxic effects of MPP+ are the apparent and poorly understood basis for the neuronal degeneration of the striatal nigris system of the mid-brain. The enzymatic conversion of MPTP to MPP+ can be blocked by MAO-B inhibitors but this research is still in progress and not yet fully developed.

1. There are problems with L-Dopa due to its side effects and the frequency of its treatment needs.

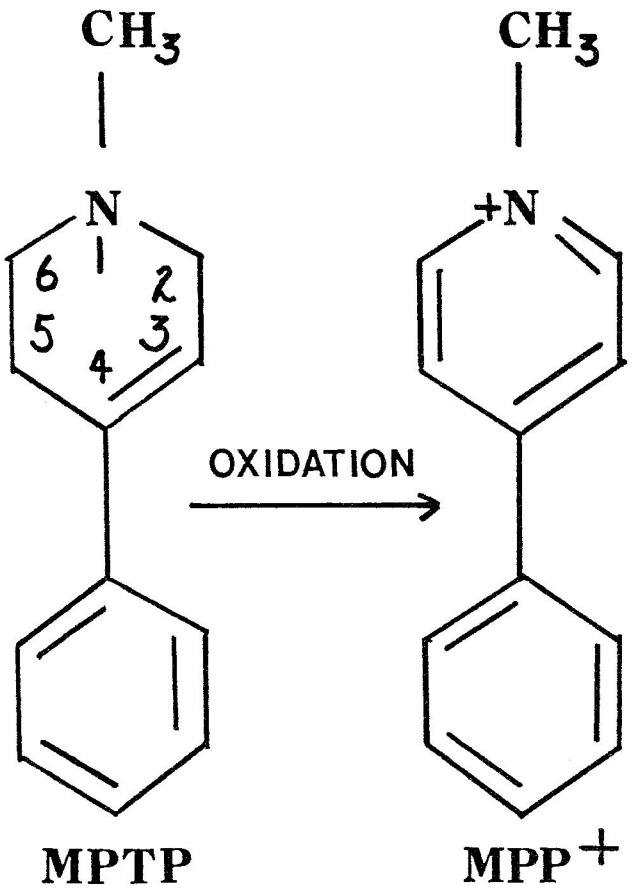


FIGURE 5

PHENCYCLIDINE (PCP)

Classification

Phencyclidine has its own classification of the arylcyclohexamines as it contains unique pharmacologic properties unto itself. It has both CNS depressant and stimulant effects as well as hallucinogenic and anaesthetic properties as well.

PCP, 1-(phenylcyclohexyl) piperidine hydrochloride, has a variety of street names including: KJ, crystal, killer weed, THC, angel dust, and blast. There is a known contaminant as a result of poor synthesis of PCP and this is PCC (1-piperidine-cyclohexanecarbonile). This contaminant is highly psychoactive and has many adverse reactions to its ingestion including nausea, vomiting, abdominal cramping. A derivative of PCP, known as TCP, (1-(1-(2-thienyl)cycohexyl)piperidine hydrochloride), is also known to be readily available to users. This analog is more potent than PCP and thus titration of its use by unknowing users is most improbable. There are about 30 other analogs to PCP, all containing the same pharmacologic properties but where quality controls are absent. Below are some of the analogs.

- PCA: 1-phenylcyclohexylamine
- NMPCA: N-methyl-1-phenylcyclohexylamine
- PCE: N-ethyl-1-phenyclyclohexylamine
- NsBPCA: N-(s-butyl)-1-phenylcyclohexylamine
- PCPY: 1(1-phenycyclohexyl) pyrrolidine
- TCP: 1-(1-1-)2-thienyl) cyclohexyl) pyrrolidine
- SKF-10,047: N-allylnormetazocine

Kinetics

PCP is a relatively simple molecule with a rigid three ring structure. It is a highly lipid soluble and is absorbed well from any site. It acts in various capacities on various parts of both the neurologic and autonomous systems. For example, it is rapidly metabolized and excreted from adipose tissue yet concentrates in much greater amounts with longevity of action within the brain. The greater amount of PCP used, the longer the action occurs. This is probably due to the fact that since PCP is attracted to acidophilic bio-environments it is secreted back into the acid of the stomach from the blood. When the PCP meets the alkaline conditions of the intestines, it is reabsorbed and continues to effect the CNS. Spinal fluid is slightly more acidic and so PCP concentrates there also gaining access to the brain. Although brain uptake of PCP is slower than the redistribution into adipose tissue, the lipid composition of brain

matter results in tissue concentrations of PCP greater and longer lasting than those found in blood.

CNS Effects

PCP causes numerous neurologic and autonomous manifestations concurrently. It is the only psychoactive that effects all known neurotransmitters at the same time. Consequently, one hears of a variety of user responses to the drug, from anesthetic-like highs to hallucinogenic through stimulation effects. The neurologic signs of PCP intoxication include nystagmus (lateral and horizontal), gait ataxia, dysarthria, muscle rigidity, convulsions, and eyes-open coma resulting from large amounts taken. Autonomic findings include hyperpraxia, hypertension, profuse diaphoresis, tachycardia, and gastrointestinal atony.

PCP produces profound effects on the levels of neurologic, autonomic, and behavioral functioning due to its known influences on the neurotransmitters of dopamine, serotonin, GABA, catecholamine, and acetylcholine systems. PCP inhibits the re-uptake of dopamine, norepinephrine, and serotonin in the CNS. PCP also possesses central anticholinergic properties. Because it acts like a dopamine antagonist, at subanesthetic doses, the behavioral toxicity mimics very closely the primary symptoms of schizophrenia (especially the paranoid type although catatonia has been seen on occasion).

Chronic users of PCP can develop an organic brain dysfunction which continues long after the cessation of the drug. This syndrome is characterized by memory gaps, disorientation, visual disturbances, and speech impediments.

At small doses, PCP illicits staggering gait, slurred speech, nystagmus, and numbness of the extremities. At increased doses there include unpredictable often hostile behavior, stupor and coma.

Prolonged periods of PCP use can produce symptoms of paranoia, hallucinations (primarily auditory), violent and bizarre behavior, anxiety, and severe depression. Post-addiction syndrome includes a clinically manifested depression. There is also evidence of a withdrawal period (from 7 to 10 days) due to the probability of a specialized PCP receptor site which interacts with the signa opioid

receptor site within the mesolimbic system of the brain (Quirion et al., 1983) (see Figures 6 & 7).

Patterns of Use

PCP is smoked, snorted, injected and eaten. Because it is tasteless and odorless, and is inexpensive to manufacture, it can be masked as any other type of drug or used as a "lacing" compound. We have seen that drugs supposed to be THC, LSD, high grade marijuana, and even cocaine, can have amounts of PCP in their contents. The usual route of administration is through smoking the PCP in either a rolled "joint" made from parsley, or from thick paper cigarettes. However, more and more users are beginning to inject the substance as well as use it more with other psychoactives. The most recent combination of PCP is in a freebase form with cocaine. Instead of calling it "crack," it is known as "spacebase" or "ghostbusters." We do not yet know the medical consequences of the synergism involved with the various PCP combinations and drug interactions.

Treatment Suggestions

Acute Phase of PCP Intoxication: For the acute stages of PCP intoxication the following treatment direction is a recommended procedure:

1. Since there are no antagonists for PCP, treatment procedures are symptomatic.
2. A toxic screen for the presence of other drugs in the system is suggested.
3. Close observation and monitoring of patient's vital signs is essential along with staying alert for respiratory depression.
4. Reduce all sensory stimulation (i.e., lights, noises, people, and remove all objects which might be harmful). Minimal contact should occur. Avoid all types of intense confrontational situations and employ standardized crisis intervention technique.
5. The phenothiezines are contraindicated during acute phase of

PCP intoxication as they tend tho exacerbate PCP's anticholinergic actions and have been seen to produce hypotension.

6. Haloperidol at 5mg i.m. hourly until patient is stabilized has been a recommendation for the control of the highly agitated patient.
7. Where seizures are present, diazepam is carefully administered at 10mg i.v. dose levels. Closely monitor this procedure as diazepam can interfere with the process of toxic elimination and thus prolong the state of intoxication.
8. The excretion of PCP can be enhanced by urine acidification to a ph level of five or less. However, caution is indicated by the following: (a) where liver disease or renal dysfunction is found, acidification is contraindicated; (b) excretion may be severely affected by the presence of other drugs so a toxic screen is important.
9. If hypertension is seen in diazoxide, hydralazine or propranolol are recommendations.
10. For patients who are comatose, the recommended treatment direction is the administration of ammonium chloride i.v. 2.75mEq/kg as 1 to 2% solution in saline. Monitor serum potassium levels, blood ammonia levels, electrolytes, blood gases, and ph levels.
11. Gastric lavage and suctioning is recommended until the patient is out of coma.

During waking state where stability has been restored, a careful psychosocial assessment is recommended to adequately plan for subsequent follow-up treatment.

It should be noted that these are the procedures for acute phases of PCP intoxication. When the patient is not under the influence, these measures should be discontinued.

Post-Intoxication Phase of PCP Treatment

Chronic severely affected PCP addicts are not very good candidates for outpatient forms of treatment. Because of the nature of the drug and its behavioral, neurologic, and autonomic effects, outpatient status for the new PCP patient is not an optimal therapeutic endeavor.

PHENCYCLIDINE (PCP) TOXIC EFFECTS

Signs and Symptoms of Street Dosages

Confusional State
dose: 5 mg.
blank stare appearance
nystagmus (jerky eye movements)
gait ataxia (cannot walk heel to toe)
disorganized thinking
difficulty speaking
muscle rigidity
respiration and blood pressure elevated
poor time estimation

Coma
dose: 20 mg.
unresponsive/immobile
eyes may be open
nystagmus
repetitive motor
movements
muscle rigidity
respiration and blood pressure elevated
slowed EEG (theta/delta)

Overdose
dose: 100mg.
prolonged coma
high blood pressure
high body temperature
tearing
salivation
facial grimacing
seizures

General Behavioral and Psychological Symptoms

Disorientation	Changes in body image
Thought disorder	Extreme anxiety
Estrangement/loneliness	Drifting in and out of consciousness
Depersonalization	Depression/suicidal tendency
Agitation	Hallucinations (auditory/visual)
Amnesia	Inability to speak coherently

FIGURE 6

FIGURE 6 (continued)

DIAGNOSIS OF PHENCYCLIDINE TOXICITY
(physical symptoms are dose-dependent)

PSYCHOLOGICAL

Low Dose Effects
- Amnesia for the episode
- Anxiety, agitation
- Body image distortion
- Depersonalization
- Euphoria (at low doses)
- Disordered thought processes
- Schizophreniform psychosis
- Hallucinations (usually auditory)
- Aggressive or self-destructive behavior
- Bizarre behavior
- Depression

High Dose Effects
- Characterized by prolonged recovery
- Alternating periods of sleep & awakening
- Similar psychological effects seen in lower dose states.

CARDIOVASCULAR
- *Elevated blood pressure (hypertensive crisis may occur)
- Pulse normal or slightly increased

AUTONOMIC
- Diaphoresis, salivation, flushing, lacrimation

DIAGNOSTIC AIDS
- EEG: Stockard et al. (1976) (describe specific EEG findings characterized by *rhythmic theta activity sometimes interrupted by periodic slow or sharp wave complexes.
- Complete Drug Screen of Blood and Urine also important to rule out presence of other drugs (salicylates, barbiturates)

*These findings are characteristic

DIAGNOSIS OF PHENCYCLIDINE TOXICITY
(physical symptoms are dose-dependent)

NEUROLOGICAL

Low Dose Effects
- *Nystagmus, horizontal & vertical, (may persist for several days)
- Variable pupil size (usually myoptic), but reactive
- Blurred vision
- Diminished pain, proprioception and temperature sensation
- *Gait ataxia
- *Increased deep tendon reflexes/clonus
- Tremors
- *Muscle rigidity
- Inability to speak
- "Blank stare" appearance
- Confusion, disorientation

High Dose Effects
- Coma (12 hours to several days)
- Eyes open
- *Spontaneous nystagmus
- Laryngeal - pharyngeal reflexes intact
- Opisthotonus or decorticate posturing
- *Increased deep tendon reflexes
- *Muscle rigidity
- Convulsions
- Hyperpyrexia
- Decreased rate and depth of respiration
- Respiratory arrest

FIGURE 7

As is usual, introducing the patient to the NA/AA program is included in the treatment of choice. Inpatient treatment staff may wish to accompany the patient to any outside NA/AA meetings as post-intoxication effects include memory loss, disorientation, mood swings and impulsiveness. These occurrences could certainly get in the way of the patient attempting to make his or her way to a program meeting outside of the hospital or clinic.

For inpatient treatment of the PCP addict, where drug elimination has already begun, there are some important points to make regarding procedures. Because PCP *does* ionize within the physiologic

urine ph range, acidification and forced diuresis measures can enhance the elimination of the drug. As such, ammonium chloride or cranberry juice, and mega doses of ascorbic acid are indicated for the duration of seven to 14 days upon admission to the facility (provided the patient has no history of hepatic or renal dysfunction). Although post-intoxication acidification procedures are not conclusive, they certainly will not harm the patient. Assisting PCP metabolite excretion through the mentioned procedure is a good measure to take at this point based on our current understanding. Rather, a therapeutic focus should be on basic life skills development with concrete readily attainable short-term treatment goals.

Because of the behavioral toxicity of PCP, confrontational (attack) methods sometimes employed by therapeutic communities (TCs) are contraindicated as they can only serve to frustrate an already stressful and delicate situation. Abstract ideology and higher cognitive intellectual situations should be avoided for the first few weeks of admission. These include expecting the new patient to memorize an abundance of facility rules and policies, conceptualizing a thorough understanding of a "higher power," meditation, beginning an inventory process, or other abstract activities that require a reasonable amount of personal insight and ability to internalize new concepts.

It is also recommended that physical exercise be at a minimum for the first few weeks. Because of the absorption and elimination properties of PCP, it is possible for the patient to have a drug-induced "flashback" as a result of the redistribution of PCP in the system. Weight lifting, volleyball, swimming, jogging, and other forms of rigorous exercise should be restricted for a period of time.

Inpatient facilities require a flexibility within their structure to account for programmatic modifications depending on the type of chemically dependent patient. Many times, through a misunderstanding of the nature of PCP, the patient gets neglected, ostracized, or required to engage in the traditional modes of treatment typically reserved for "street hypes" when in fact these modes are clinically contraindicated and work against the patient's recovery.

The treatment of choice, notwithstanding, is still the exposure of the patient to the NA/AA program. The modification however, is in the pace or the tempo at which this process is given. Perhaps the

key words here are to slow down for a few weeks the usual treatment momentum that is provided to patients having other primary drug dependencies. Symptoms of post-intoxication do gradually reduce in this time frame. However, other symptoms may exist for six to eight weeks duration. These have included periods of disorientation, random memory loss, confusional states (transient), feelings of depersonalization, and depression (although depression is common to many addicts in treatment and not highlighted for only PCP). Schizophrenic-like behavior for up to six weeks after acute intoxication can exist (Aniline and Pitts, 1982).

Helping the individual to assemble a working knowledge and personal understanding of the nature of the disease of addiction is critical in the recovery process. The program of NA/AA does this well. It is only during the first few weeks that this process should be more loosely applied and that as the weeks in treatment progress, the therapeutic process can pace the patient more intensely in his or her recovery.

MDA/MDMA

Classification

MDA and MDMA are classified as hallucinogens but having stimulant properties. MDA, (93-4-methylenedioxyamphetamine) and MDMA, (MDA's N-methyl analog) both produce stimulant and psychotomimetic effects in users (see Figure 8). Street names of MDMA include Adam, Ecstasy, XTC, M&M, MDM, and E. MDMA is considered pharmacologically along with other drugs of the phenylethylamines (which include mescaline, DOM or STP, and myriusticin).

Kinetics

The exact pharmacokinetic action of the MDAs is not known. However, because the parent compound of MDMA is methamphetamine, we infer that the substance is probably ionized in the acidity of the stomach and is well absorbed through the alkalinity of the intestines. Because of the mechanism of action, the MDAs are short acting compounds (typically dose of 120mg provides about 90 min-

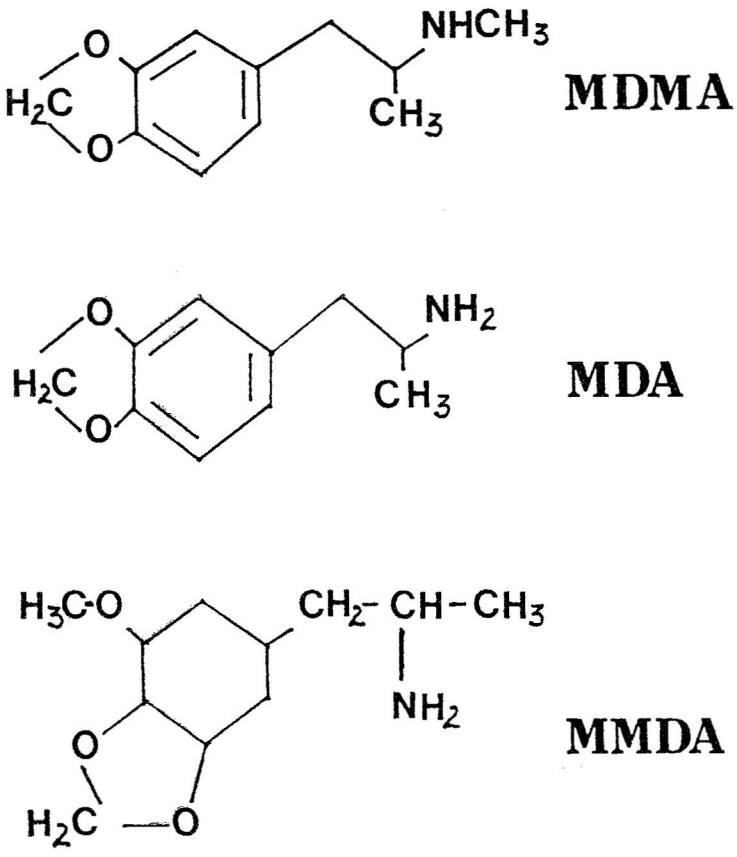


FIGURE 8

utes of psychoactive effect), the metabolism and excretion ratios are quick.

Whether metabolites contain a toxic basis or not is yet to be found. MDAs are inactivated both by demethylation and through the monomine oxidase system.

CNS Effects

The phenylethylamines are structurally related to the neurotransmitter dopamine and norepinephrine as well as amphetamine. Accordingly, they stimulate the reticular activating system of the brainstem impacting effects at the synaptic junctions. Methamphetamine, the parent compound of MDMA, has been shown to cause degeneration within the dopaminergic system within the mid-brain area. However, whether MDMA also produces a clinical neurologic pathology is not known. There is also some indication that the MDAs effect the serotonergic system of the brainstem area and along the mesolimic system which results in distorted functioning of mood, libidinal activity, sleep regulation, sensitivity to pain and aggression. It is inferred that the effected serotonergic systems are the reasons why users experience serenity, elevated sensuality, increased libido, lethargy, and hallucinations. Other CNS responses are elevated blood pressure (in excess of 15mm/HG at onset of drug action), bruxism, nystagmus, heightened sensitivity to auditory and visual stimuli, cephalalgia, arrhythmia, diaphosesis, anxiety, and for unknown reasons, the MDAs activate latent infections within the genital-urinary tract of women. Tolerance and physiologic dependence are not conclusive at this time. However, if the body converts the methamphetamine parent compound to amphetamine, tolerance and dependence are suspected.

Patterns of Use

Although the MDAs have been around for over a decade now, their popularity has only been in the past few years. The MDAs were first produced in 1962 by a chemist, Alexander Shulgrin (also produced STP or DOM, a powerful and popular psychedelic of the 1960s).

The MDAs have been used by the gay communities during the 1970s and most recently by college kids, "yuppie" groups, and adolescents. It is not a new compound. As David Smith, MD, of the Haight-Ashbury Clinic in San Francisco, said,

> It's marketing . . . there are a lot of things that have been on the shelf for a long time and are getting dusted off. You take an old drug, give it a new name, and introduce it to a new culture that has money, tell them it's going to do wonderful things for their social and sex life and jack up the price.

MDA/MDMA are considerably less expensive than cocaine which is another factor in their popularity. Cocaine costs about $150 per gram, while MDMA costs around $45.

Already there has been an identified MDA analog called MDE, (2-ethylamino-1-(3.4.methylenedioxyphenyl)-propane). It is conceivable that more are on their way since the marketing and market are right. MDE is not on the DEA's restricted list since the compound is so new and the DEA has not yet responded to its scheduling.

Treatment Issues

This presenter has never treated nor heard of any other clinician treating a person having a primary drug of dependence of MDA/MDMA. However, when during the course of treatment for other drug combinations, and where the MDAs have been used by the patient, education on the compound's toxic effects is important. This drug is shrouded by a lot of confusion, misinterpretations, and misunderstandings. Therefore, and because we never underestimate the addict's inherent ability to rationalize a justification for continued use, it would be wise to inform the patient of clinical findings and other pertinent information with emphasis on the uncertainty of any designer drug compound.

Patients with a history of MDA use typically include two primary groups; white middle-class adolescents and white middle-class adults who are employed, like to socialize, have several relationships, are crime free, and are looking for meaning in life. Frequently users combine the MDAs with alcohol and cocaine, although not necessarily concurrently. The myth is that MDMA is used by physicians in therapy/counseling and that the drug is a "mild" hallucinogen. Since it is used by doctors and is mild, it is safe to ingest on a regular basis. This misunderstanding, coupled with a name like "Ecstasy," makes for a repeated use situation.

Typically, patients with a history of MDA/MDMA use are good candidates for outpatient treatment. This is because usually a level of socialization, insight, and motivation for treatment are generally higher than for others whose drug of choice has more debilitating consequences physiologically and physically (i.e., heroin, PCP, crack).

Treatment focus should be on the nature of the disease of addiction, who is an addict, alternative socializing and peer group plans, addressing any personal conflicts that have arisen as a result of drug involvement (i.e., financial, relationships, and subsequent guilt-depression systems), and arresting the further development of any identified addictive patterns or behavior and psychological dependence. It should be emphasized however, that there are no "purists." There are no alcohol purists, no heroin purists, no MDMA purists . . . no purists. People use a variety of chemicals and oftentimes in combination with each other. The patient's drug history, although it includes the MDAs, should also play a critical part in the defining of the treatment direction. Rarely does a patient come into treatment with a clear and simple drug use problem of only one substance. there is a battery of other chemicals that have been and are still being used. Thus, a clearer picture begins to form as to the extent and level of involvement the patient is engaged in with chemical usage. This assessment will provide the therapist information needed to modify any treatment direction to include such elements as NA/AA participation, family therapy, short-term inpatient, etc. So even though it may be doubtful that a patient with a singular history of MDMA abuse will come in to treatment, we take initial complaint, coupled with the findings of the history, and modify the treatment course as seen in the patient's response, so that an overall synthesis can occur where, through self-esteem and self-development issues can be improved to the point where further chemical abuse is eliminated.

We have only seen a few of the known controlled substances' analogs. This does not mean that the problem is over. Since the writing of this article, we have seen more analogs of PCP and an analog of methamphetamine that has caused Huntington's Chorea. The analog game has just begun. It is this clinician's opinion that we truly are just seeing the "tip of the iceberg." One can realisti-

cally expect more cases of atypical sympatomology due to adverse effects of chemical analogs. This would most certainly include analogs that are neurotoxic as well.

It is the intent of this paper to point out the medical aspects and clinical management of some known analog substances. It is perhaps an equally important intent to point out that chemical dependency treatment personnel, and the helping profession in general, maintain an acute awareness of differences in their patient populace. That is, where symptoms can be changing due to new substances and resultant pharmacokinetics or toxicologic effects. Treatment professionals simply cannot afford merely to provide treatment based out of habit or on an understanding of the addicted populace as it was 10 years ago. The advent of so many "garage laboratories" and self-made chemists, as well as the countless numbers of documented case histories of affected users reinforce this statement. Interested readers may stay apprised of this issue of controlled substances analogs through contact with this journal.

REFERENCES

Arau, Anthony. The Phencyclidine (PCP) Story. Pathway Society, Inc., 1984.

Bassuk, Ellen, L. Practitioner's Guide to Psychoactive Drugs. Plenum Medical Books. New York. 1978.

Burns, Stanley, R. The Clinical Syndrome of Striatal Dopamine Deficiency. New Eng J. Med. 1418:1421. 1985.

Cohen, Sid. The Substance Abuse Problems: Volume II. New Issues For the 1980's. The Haworth Press, Inc., New York. 1985.

Fauman, M.A. Chronic Phencyclidine (PCP) Abuse: A Psychiatric Perspective. J. Psychedelic Drugs. 12:307-315. 1980.

Gallagher, Winifred. Discover Magazine. 26-35. August, 1986.

Langston, J. William. Neurologic Complications of Drugs of Abuse. Stanford University Medical School. 1985.

Langston, J. William. Aetiology of Parkinson's Disease. The Lancet. 1457-1459. Dec 24/31. 1983.

Langston, J. William. The Case of the Tainted Heroin. The Sciences. New York Academy of Sciences. 34-40. 1985.

Lewin, Roger. Clinical Trial for Parkinson's Disease. Science. Vol. 230. 527-528.

Marwah, J. Candidate Mechanisms Underlying Phencyclidine Induced Psychosis: An Electrophysical, Behavioral, and Biochemical Study. Biol. Psychiatry. 17:155-198. 1982.

McCarron, M.N. Acute Phencyclidine Intoxication: Clinical Patterns, Complications, and treatment. Ann Emerg. Med. 10:290-297. 1981.
Radcliff, A. The Pharmer's Almanac. Pharmacology of Drugs. M.A.C. 1985.
Ruttenber, A.J. et al. Meperidine Analog Exposure In California Narcotics Abusers: Initial Epidemiologic Findings. Centers for Disease Control. 1985.
Seymour, R.B. Is Ecstasy Spelled MDMA? Longmeadow Press, Stamford. 1985.
Shafer, J. Designer Drugs. Science. 85. 62-67.
Stanford, Mark W. PCP Abuse: Aspects and Community Issues. Pathway Society, Inc. 1987.
Shulgin, A.T. J. Anal. Tox. 6. 71-75. 1982.

CONTACT ADDRESSES:

Centers For Disease Control
Division of Chronic Disease Control
Altanta, GA 30333
(404) 452-4068
Paul L. Garbe, DVM, MPH

Institute For Medical Research
2260 Clove Drive
San Jose, CA 95129
(408) 299-8296
J. William Langston, MD

Pathway Society, Inc.
1659 Scott Blvd. #30
Santa Clara, CA 95051
(408) 244-1834
Mark W. Stanford, PhD