STIMULANTS

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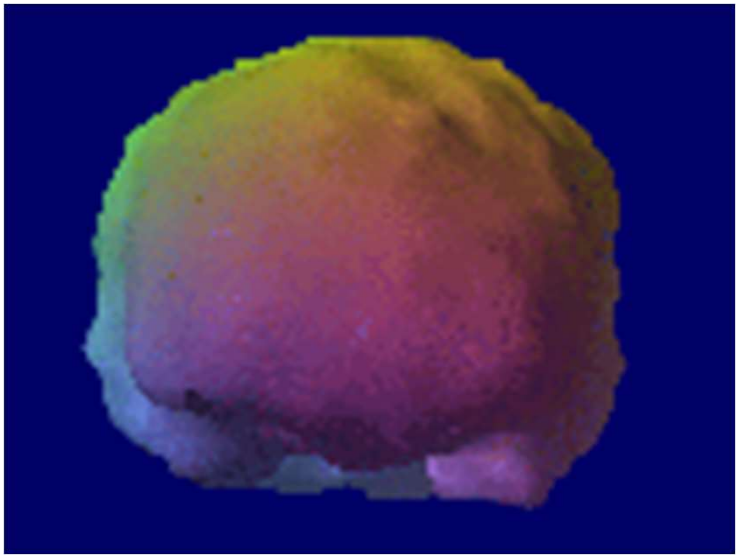
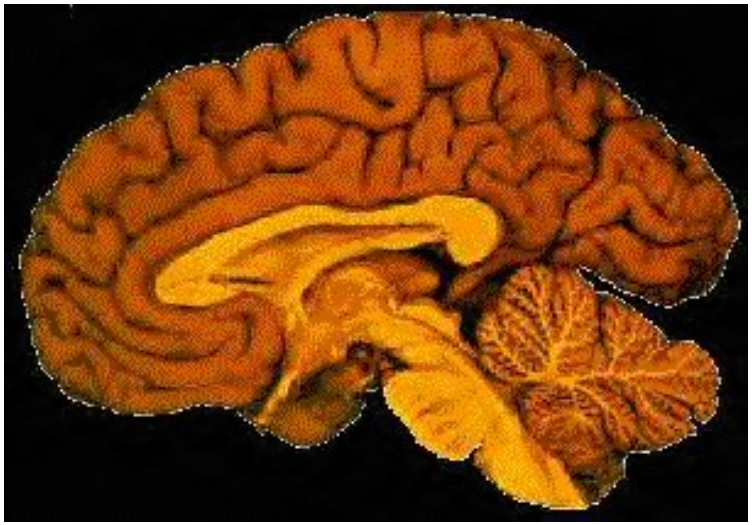
Background

- Stimulants have been used by humans for thousands of years to increase energy
- Plant-derived stimulants have been refined and new drugs developed to increase potency and duration
- As potency increases negative effects become apparent.





History of Stimulant Use

3000 B.C.	Ma –Huang
0 A.D.	Coca leaf chewing and coca tea (ephedra)
1860	Cocaine Isolated
1887	Amphetamine Synthesized
1914	Harrison Narcotic Act
	◆ MDMA
1919	Methamphetamine
1930s	Benzedrine Inhaler
1959	Benzedrine Banned
1989	Crack

STIMULANT DRUGS

Plant-Derived

- Caffeine
- Cocaine
- Ephedra
- Khat

Synthetic

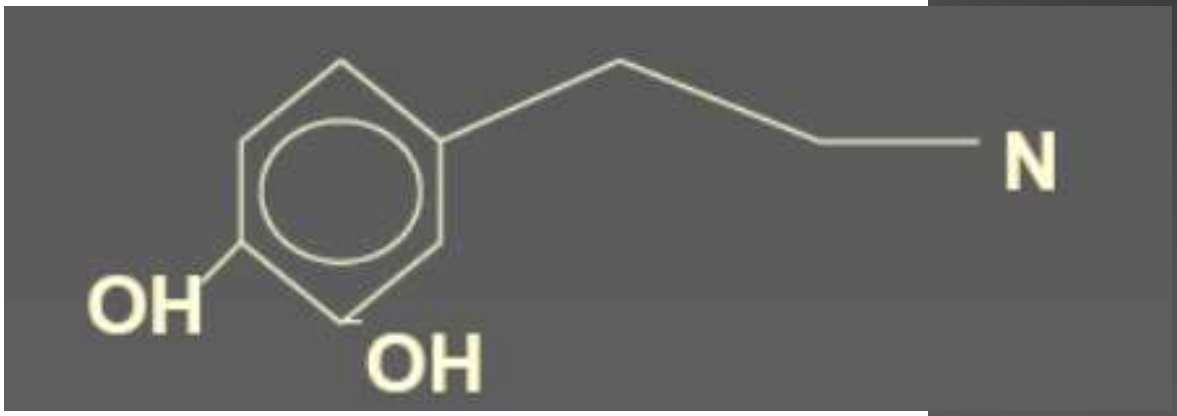
- Amphetamine
- Methamphetamine
- Methylphenidate
- Mazindol
- Phenylpropanolamine
- Ephedrine
- Pseudoephedrine
- Phenylephrine
- MDA/MDMA

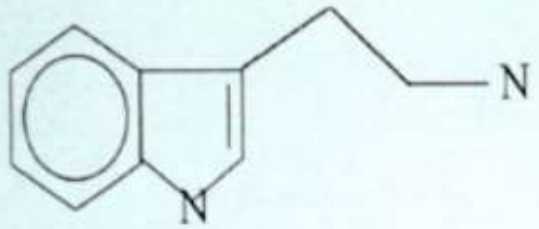
Stimulants

- **Cocaine hydrochloride**
- **Amphetamines**
  - dextroamphetamine (Dexedrine)
  - l-lysine-d-amphetamine (Vyvanse)
  - amphetamine sulfate (Adderall)
  - methamphetamine (Desoxyn, Adipex)
- **Amphetamine Cogeners**
  - benzphetamine (Didrex)
  - diethylpropion (Tenuate, Tepanil)
  - fenfluramine (Pondimin)
  - mazindol (Masanor, Sanorex)
  - phendimetrazine(Adipost, Bontril, Prelu-2)
  - phenmetrazine (Preludin)
  - phentermine (Fastin, Adipex, Ionamine)
- **Methylphenidate (Ritalin)**
- **Pemoline (Cyclert)**
- **Phenylpropanolamine**
- **Phenylephrine**
- **Pseudoephedrine**
- **Ephedrine**
- **Caffeine/Theobromine**
- **Theophylline**
- **Epinephrine**
- **Cathine/Cathinone**

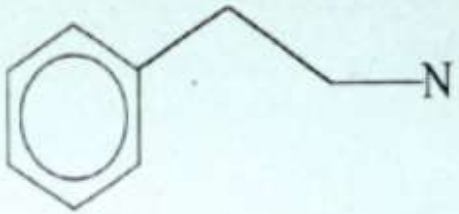
Structure and Pharmacology

- All stimulant drugs share a common basic phenylalkylamine structure
  - Additions to the phenyl group tend to increase hallucinogenic properties
  - Additions of a methyl group to the nitrogen atom tend to increase the stimulant properties

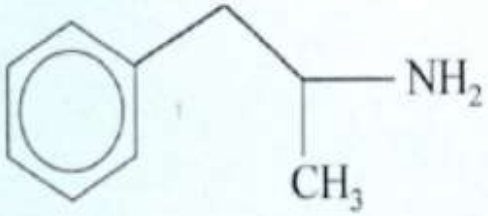




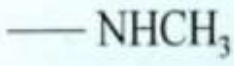
indolealkylamine



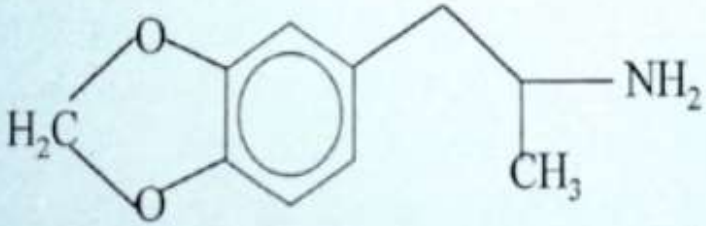
phenylethylamine



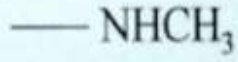
amphetamine



methamphetamine



methylenedioxyamphetamine
(MDA)



methylendioxymethamphetamine
(MDMA)

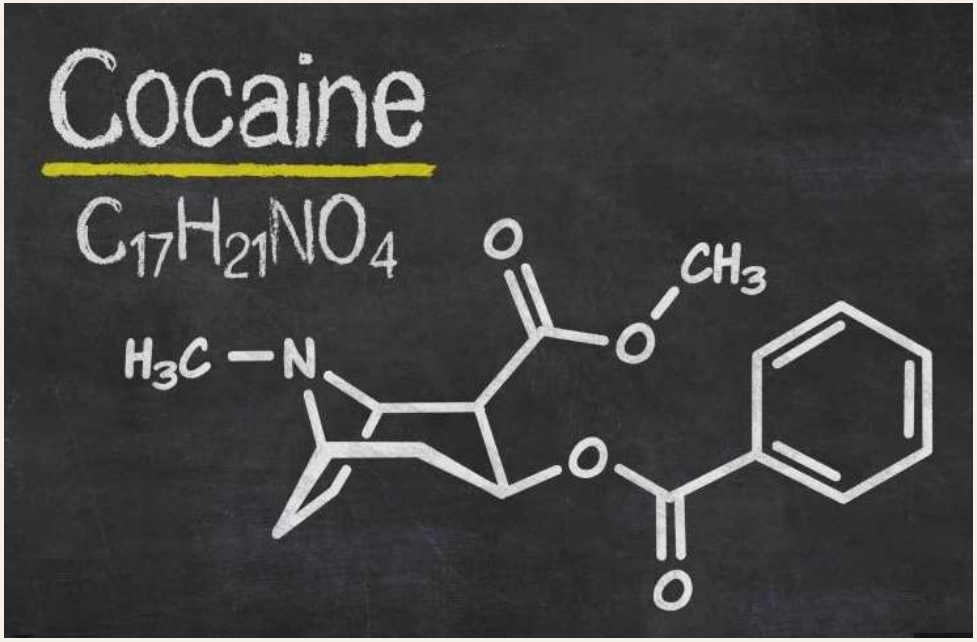
Therapeutic Uses

Cocaine is the best local anesthetic

Rx Amphetamines are limited to treatment of:

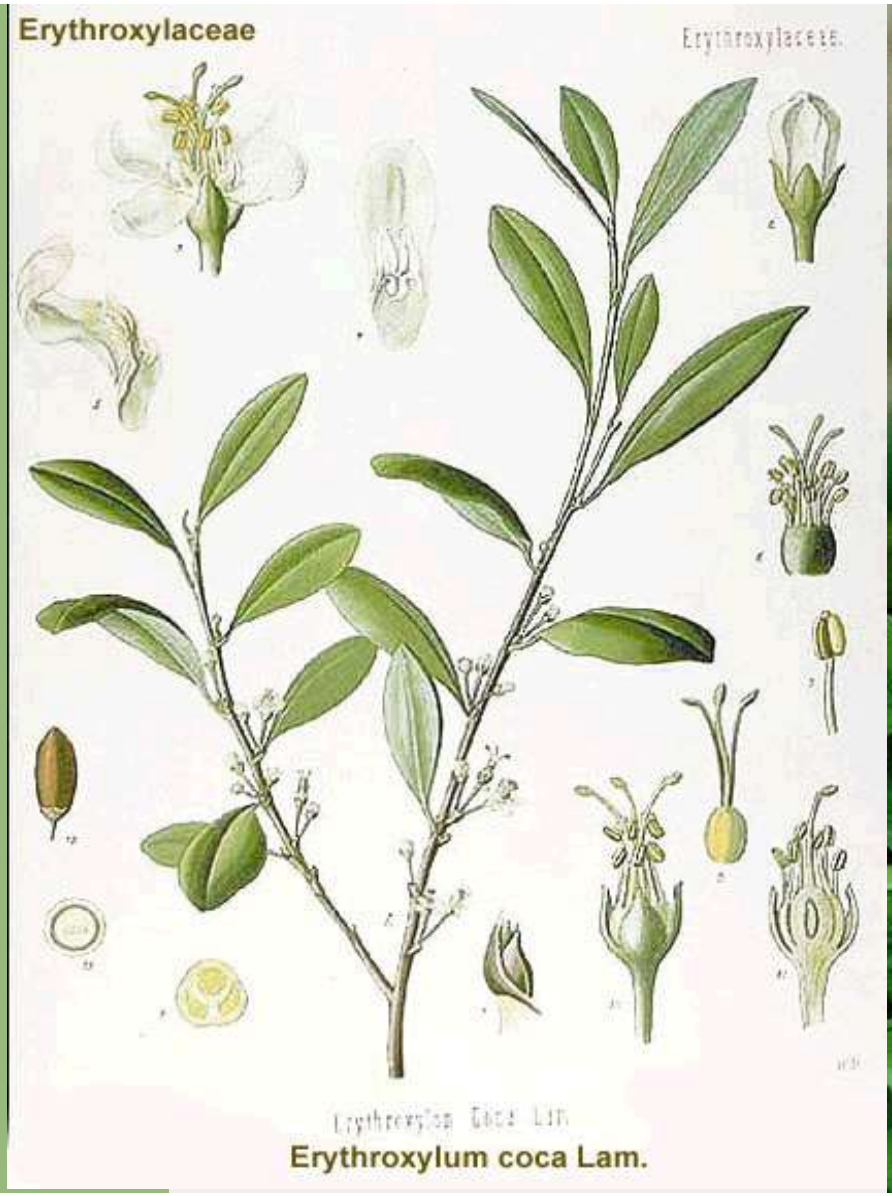
- Narcolepsy
- Childhood Hyperkinesis
- Refractory Obesity
- Headache
- Mydriatics
- Depression
- Sleep Apnea
- Decongestion
- Asthma
- Hypotension during Anesthesia
- Allergic Reactions
- Apnea in Pre-term Infants

Cocaine



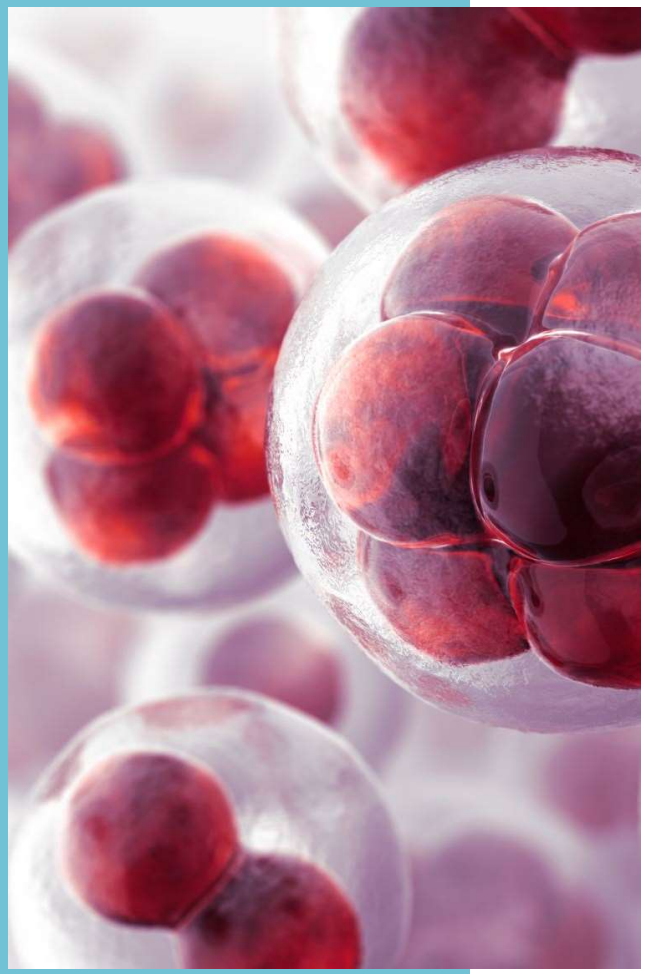
- Intranasal, smoked, oral, injection
- Street cocaine concentrations 10 to 50% (powder), >70% “rock” or “crack”
- Cocaine primary effect in brain:
  - blockage of presynaptic reuptake of neurotransmitters dopamine, serotonin and norepinephrine in the medial forebrain bundle (MFB = frontal cortex, nucleus accumbens, ventral tegmental areas)
- upregulates mu, delta, kappa opiate receptors

Erythroxylaceae



Erythroxylum coca Lam.

COCAINE



ABSORPTION, METABOLISM

1. Peak cocaine blood levels occur about 30 min after intranasal use but only after 4 min with IV use and smoking
2. Plasma half-life is very short—40 to 60 min;
   - in urine up to 36 hours
   - in brain 2-3 days
3. Liver metabolizes via CYP450 benzoyleconine and ecgonine measurable several days in urine;
   - hair samples can contain levels months later
4. Amphetamines:
   - peak levels 1-3 hours after oral
   - rapid after IV or smoking
   - Half-life from 2 to 6 hrs.

ADVERSE EFFECTS

Acute Intoxication & Overdose

CNS stimulation Increased alertness and arousal euphoria analogous to orgasm lowered seizure threshold giddiness increased libido (initially)	Grandiosity Forceful Boisterousness “bulletproof”	Poor judgment Confusion Hyperpyrexia & dyskinesias Tremors Stroke	Tachycardia Hyper- or hypotension Chest pain Arrhythmias Coronary Spasms/infarction Rhabdomyolysis with acute renal failure	Vomiting Urinary and bowel delay and retention Psychomotor agitation or retardation Muscular weakness Flushing Pupillary dilatation

Chronic Intoxication

- Down-regulation of dopamine, NE, and EPI sites
- Sense of doom or anxiety indistinguishable from panic disorder
- Pressured speech, hallucinations, delusions, paranoia, ideas of reference looking like hypomania, mania, schizophrenia, psychosis
- Lung damage: pulmonary edema, cough, black sputum, diffuse alveolar hemorrhage, “crack lung”, cardiopulmonary barotrauma (pneumomediastinum, pneumothorax, pneumopericardium), interstitial fibrosis
- Heart: Congestive heart failure

Chronic Intoxication

Abnormal menses, galactorrhea, amenorrhea, infertility, spontaneous abortions, decreased libido; spontaneous orgasm; impotence

“crack babies”(?); cocaine in breast milk 60 hrs after mother’s use

Depression, injury, violence, homicide, suicide

“risky behavior”

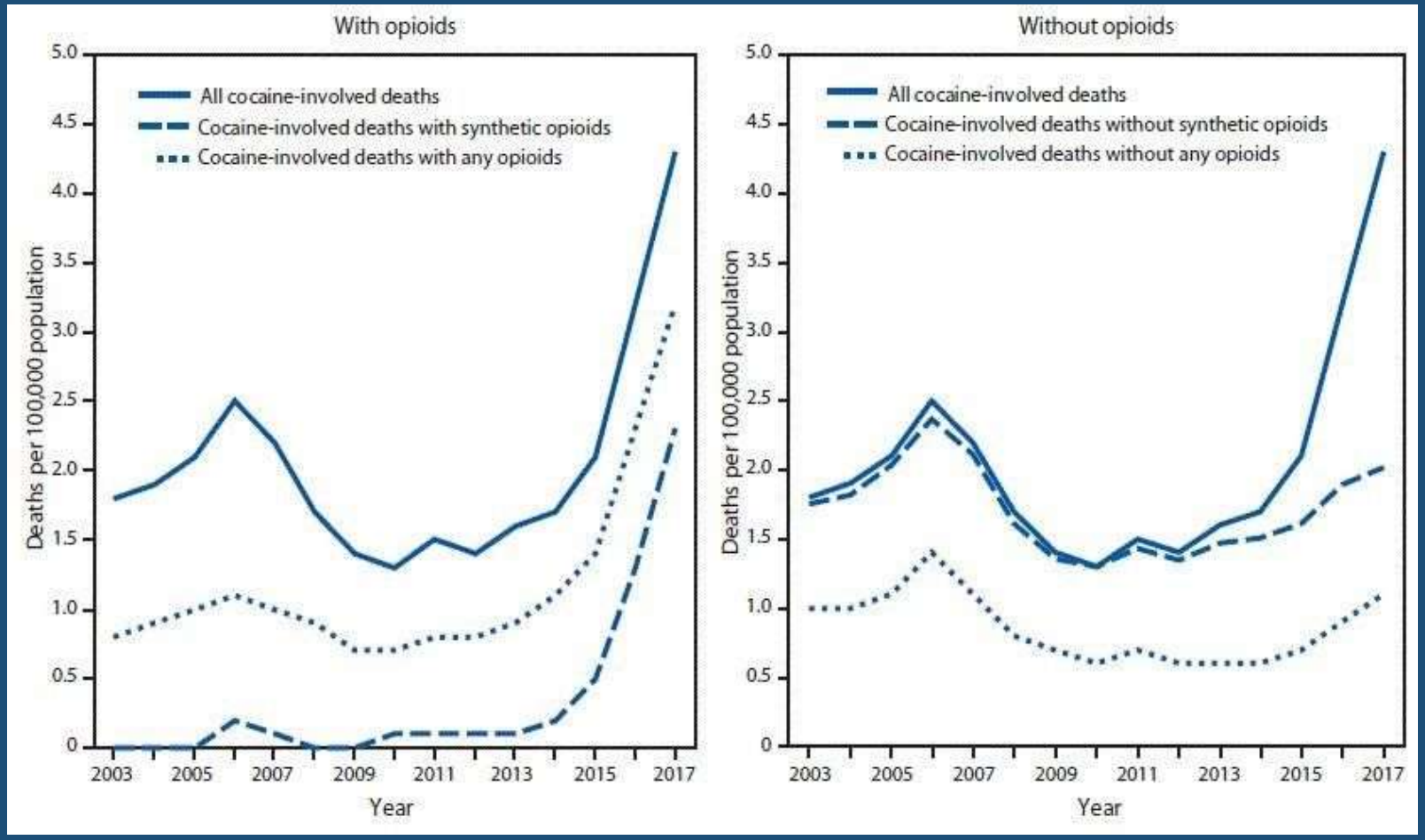
Polysubstance use/abuse--62-90% of cocaine abusers also ethanol abusers

“new drug” cocaethylene blocks dopamine reuptake and has longer half-life than cocaine. May cause greater toxicity.

Withdrawal

- DYSPHORIC MOOD
- FATIGUE
- VIVID AND UNPLEASANT DREAMS
- INSOMNIA OR HYPERSOMNIA
- INCREASED APPETITE
- PSYCHOMOTOR AGITATION OR RETARDATION
- ANHEDONIA

US Cocaine Deaths +/- Opioids



PHARMACOLOGIC THERAPIES

There are no FDA approved pharmacotherapies for the treatment of StUD.

Dopaminergic agonist	bromocriptine, amantadine
Dopaminergic antagonists	neuroleptics
Antidepressants	SSRI's, desipramine/imipramine, MAOI's, bupropion
Stimulants	methylphenidate, phenmetrazine
Anticonvulsants	carbamazepine, valproic acid, phenytoin
Amino acids	L-dopa, L-tyrosine
Lithium	Calcium channel blockers
Opiate antagonists	naltrexone, nalmephene
Disulfiram/Antabuse	inhibits dopamine degradation
Cocaine Vaccine	*(Arch Gen Psychiatry. 2009;66(10):1116-1123. doi:10.1001/archgenpsychiatry.2009.128)*

*Some of these agents do work if they are prescribed for appropriate co-morbid disorders

PHARMACOLOGIC THERAPIES

- Bupropion is a dual dopamine and norepinephrine reuptake inhibitor that is FDA approved 4 for the treatment of major depressive disorder, seasonal affective disorder and smoking cessation.
- Clinicians can give bupropion additional consideration for patients with a co-occurring tobacco use disorder as it can also reduce tobacco use.
- Modafinil is a wakefulness-promoting medication used in the treatment of narcolepsy, obstructive sleep apnea and shift work sleep disorder.
- Topiramate is an anticonvulsant medication, FDA approved for the treatment of epilepsy and migraine.
- Because topiramate has been shown to reduce alcohol use and is utilized off-label for treatment of AUD, this combination treatment could be given additional consideration for patients with co-occurring cocaine and alcohol use disorders.

PHARMACOLOGIC THERAPIES

- Topiramate + Extended-release Mixed Amphetamine Salts (MAS-ER) 2 (e.g., Adderall, Mydayis), are comprised of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, amphetamine sulfate.
- This combination could be given additional consideration for patients with co-occurring cocaine use disorder and ADHD due to the effects of Clinicians should note that thorough cardiovascular screening at baseline is important including a baseline assessment of cardiovascular function. Clinicians should monitor for signs and symptoms of cardiovascular dysfunction during the early phase of treatment.
- Known effects of psychostimulant medications on blood pressure can be managed by close patient monitoring and dose adjustment pf MAS-ER on ADHD symptoms.
- While the evidence for bupropion alone is somewhat weak in patients with ATS use disorder, two recent studies using combination bupropion and naltrexone have shown more promise in terms of stimulant use outcomes.

ADDICTION LIABILITY AND REINFORCING PROPERTIES

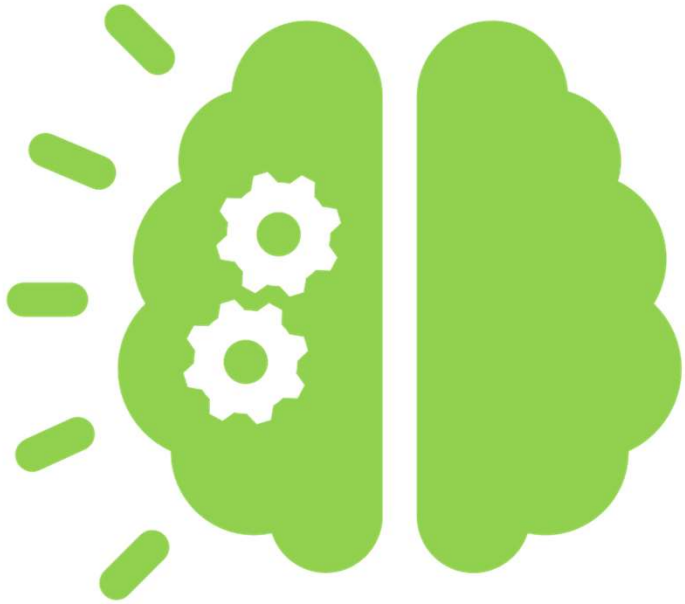
Addiction potential of cocaine is related somewhat to delivery system used

Tolerance to euphoria of cocaine develops within 1 hr. of initial dose! Thus, usually one cannot recapture the marked euphoria of the initial experiences

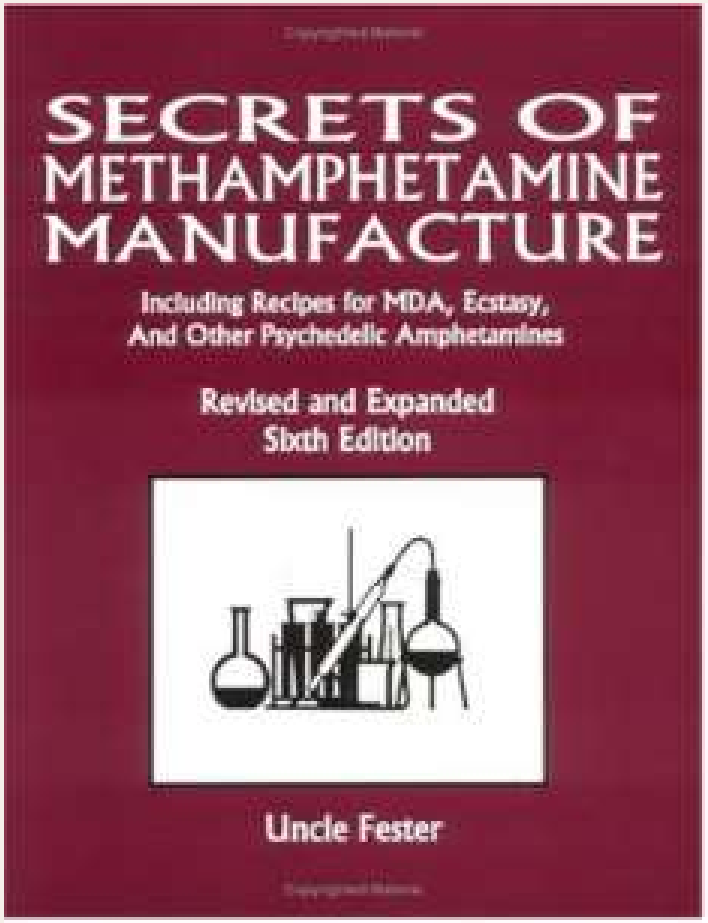
Primary activity on dopaminergic system which is the primary reinforcing system in the brain

METHAMPHETAMINE

- Methamphetamine
  - Powerful central nervous system stimulant that strongly activates multiple systems in the brain.
  - Closely related chemically to amphetamine, but the central nervous system effects of methamphetamine are greater.



Book Description

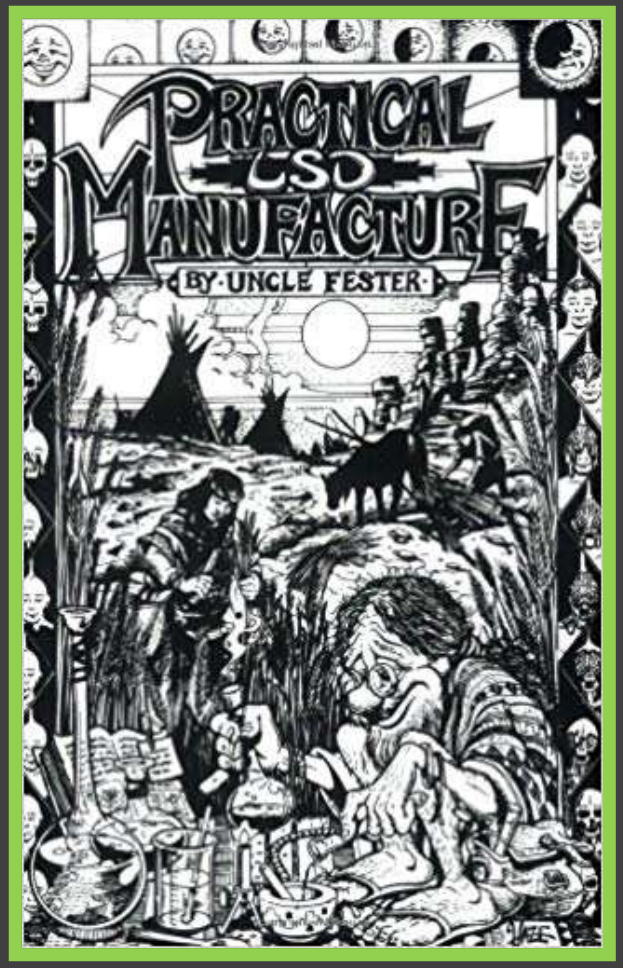


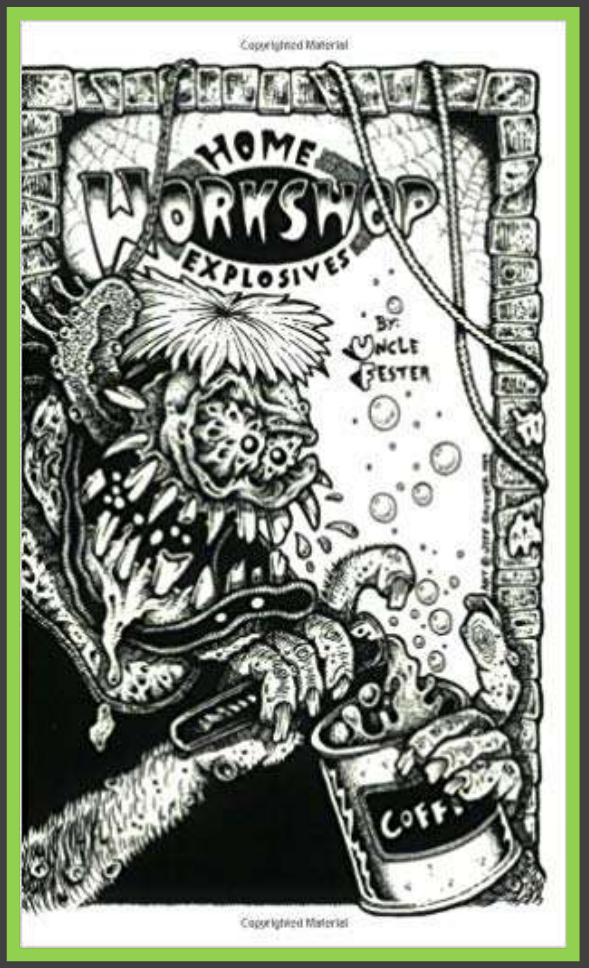
From Amazon.com

"For nearly 20 years now I have been training champions, the champions of the field of clandestine chemistry. This book is their training ground. I cover virtually every possible method of making that "food of the God's" - meth along with how to make it from commonplace materials. I also give coverage of the history of this field, so that newcomers can quickly feel like old pros."

-Uncle Fester

Other “Uncle Fester” Books





Methamphetamine: Speed

- Methamphetamine powder ranging in color from white, yellow, orange, pink, or brown.
- Color variations are due to differences in chemicals used to produce it and the expertise of the “cooker”
- Other names: shabu, crystal, crystal meth, crank, tina, yaba

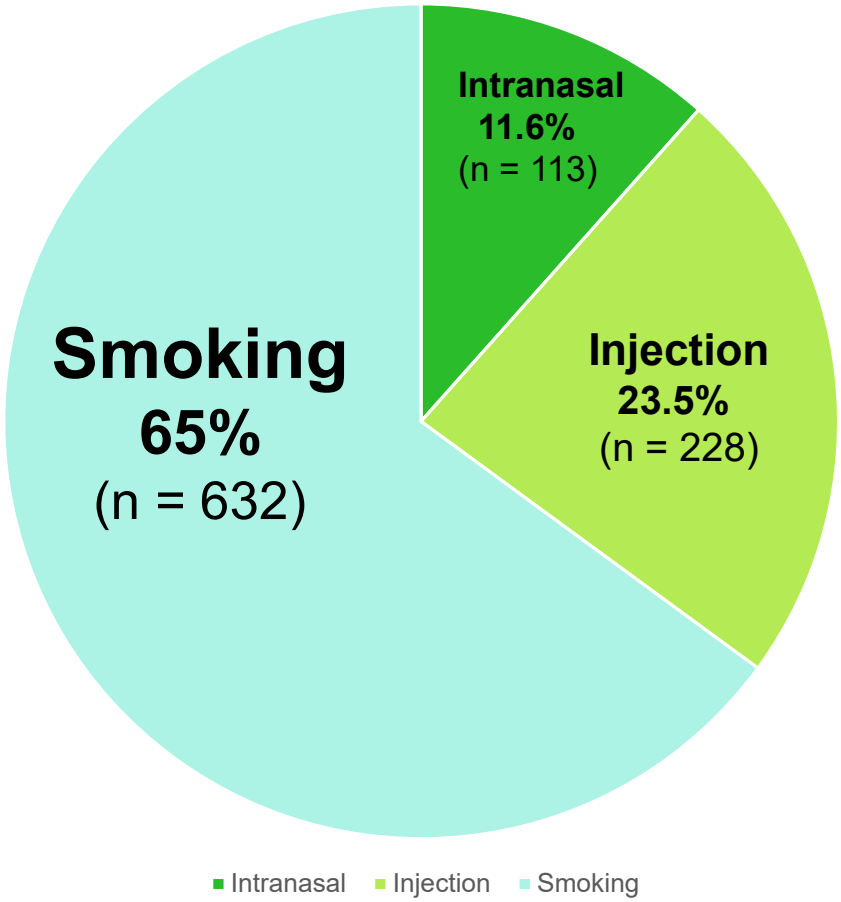
Methamphetamine: Ice

Methamphetamine Powder

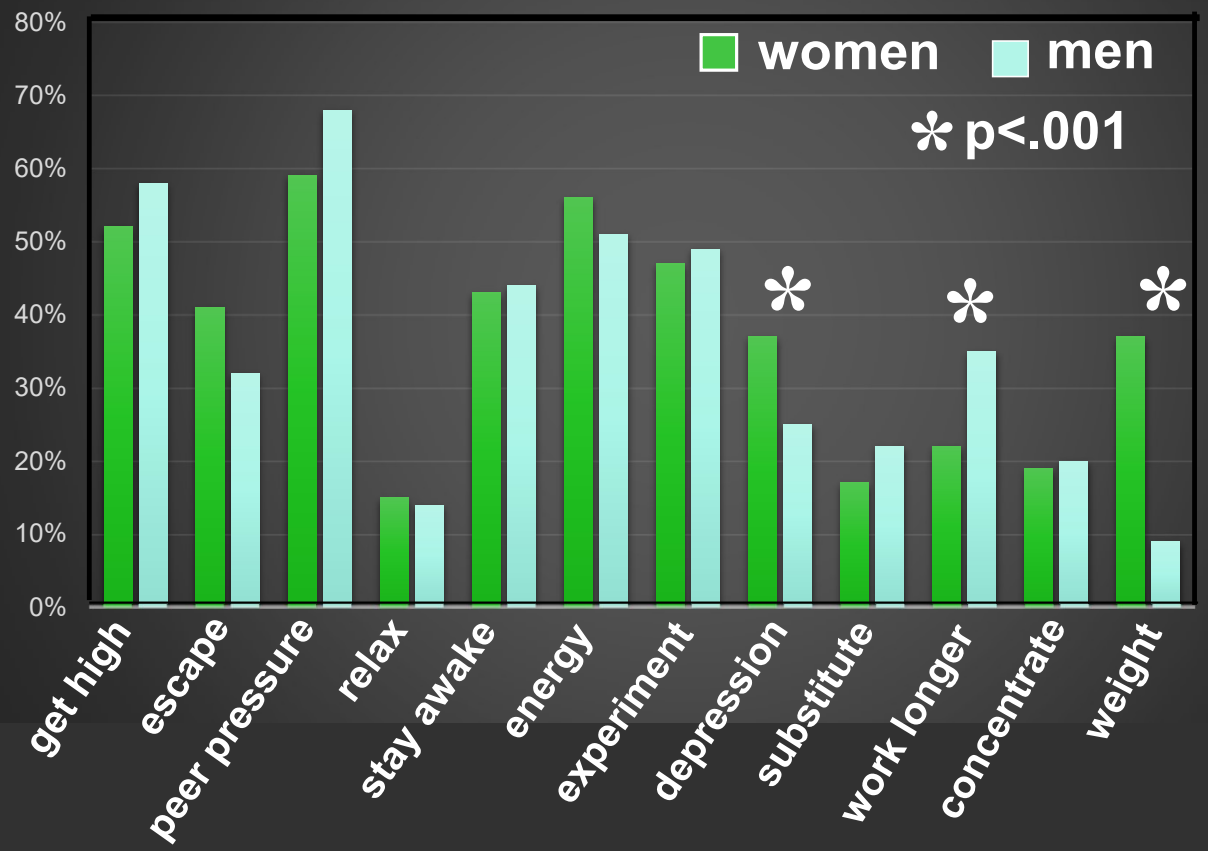
Methamphetamine Crystals

- High purity methamphetamine crystals or coarse powder
- Ranging from translucent to white, sometimes with a green, blue, or pink tinge.

Routes of Administration in Clients Seeking Treatment



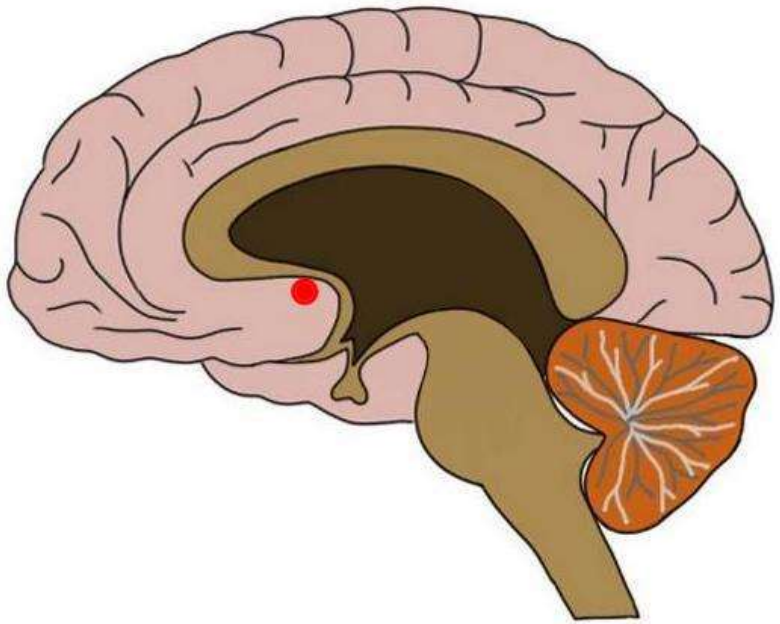
Why Start Using Methamphetamine?



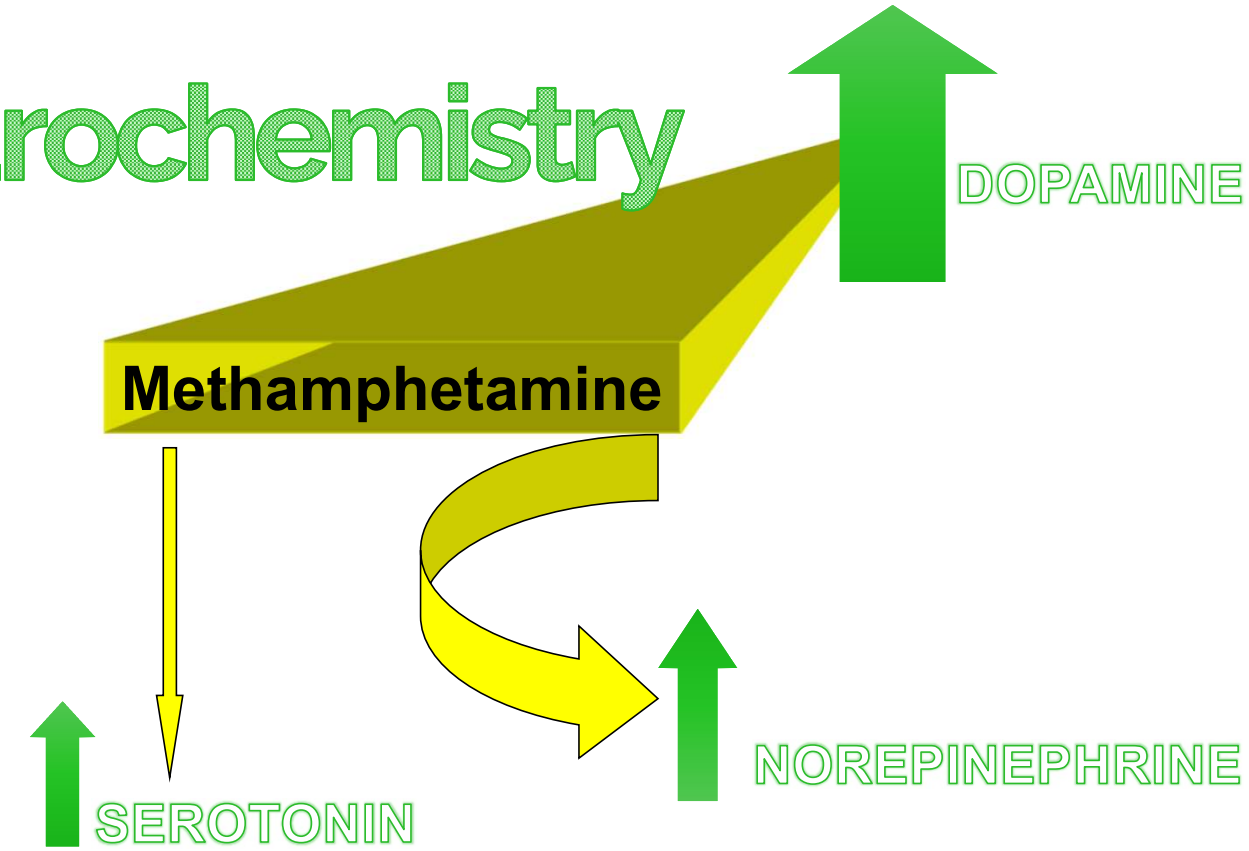
"Meth doesn't upset my stomach the way coffee does."

A Major Reason People Take a Drug is they Like What it Does to Their *Brains*

It is the amount and speed of the release of Dopamine in the *nucleus accumbens* that is most likely related to the addiction potential of a behavior, substance or drug.



Neurochemistry



Methamphetamine – *Acute Physical Effects*

INCREASES

- Energy
- Heart rate
- Pupil size
- Respiration
- Sensory acuity
- Blood pressure
- Blood glucose
- Flow of blood to muscles
- Vasoconstriction of arteries and veins

DECREASES

- Reaction Time
- Appetite
- Sleep

Methamphetamine – *Acute Psychological Effects*

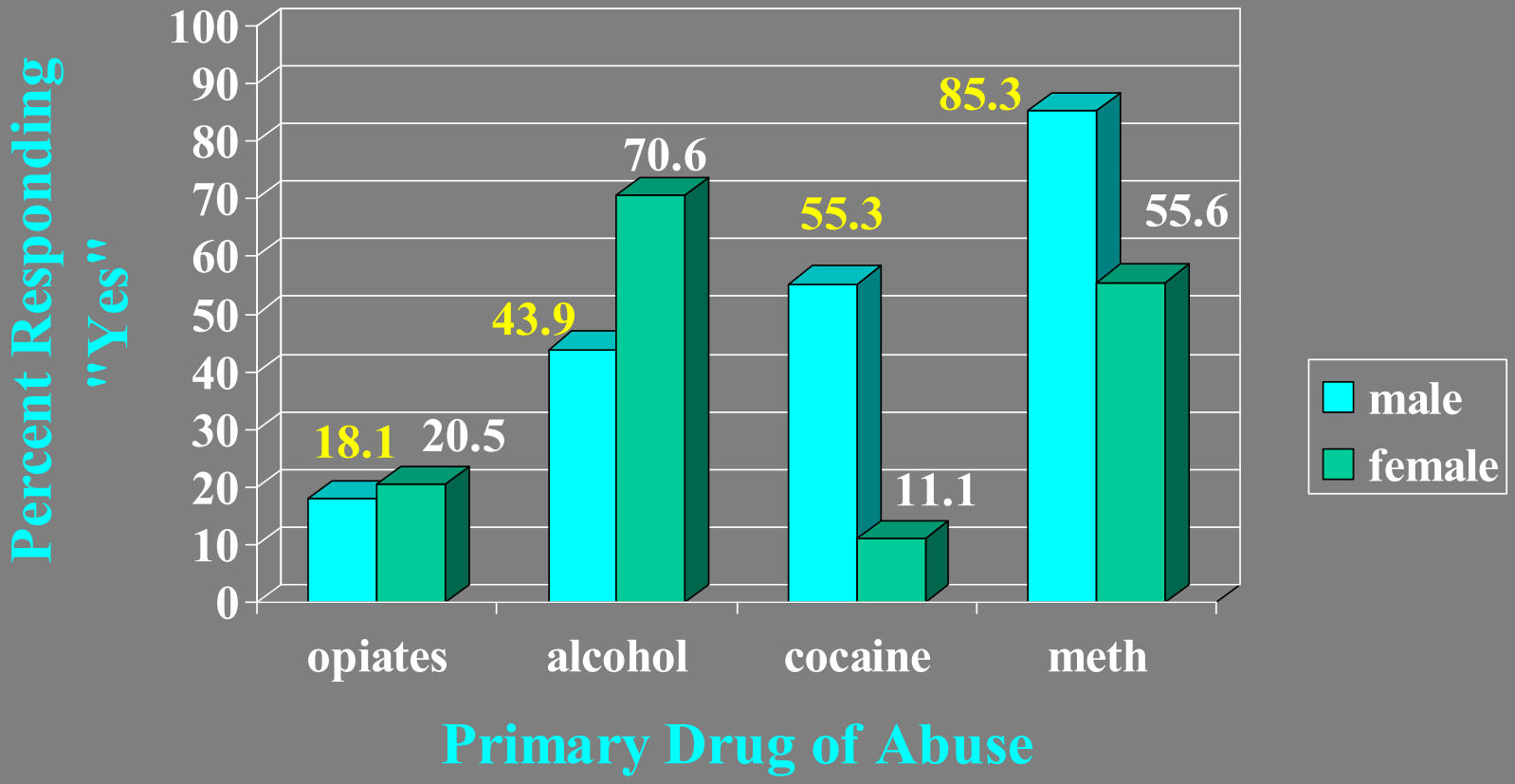
INCREASES

- Mood
- Energy
- Alertness
- Sex drive
- Confidence
- Talkativeness

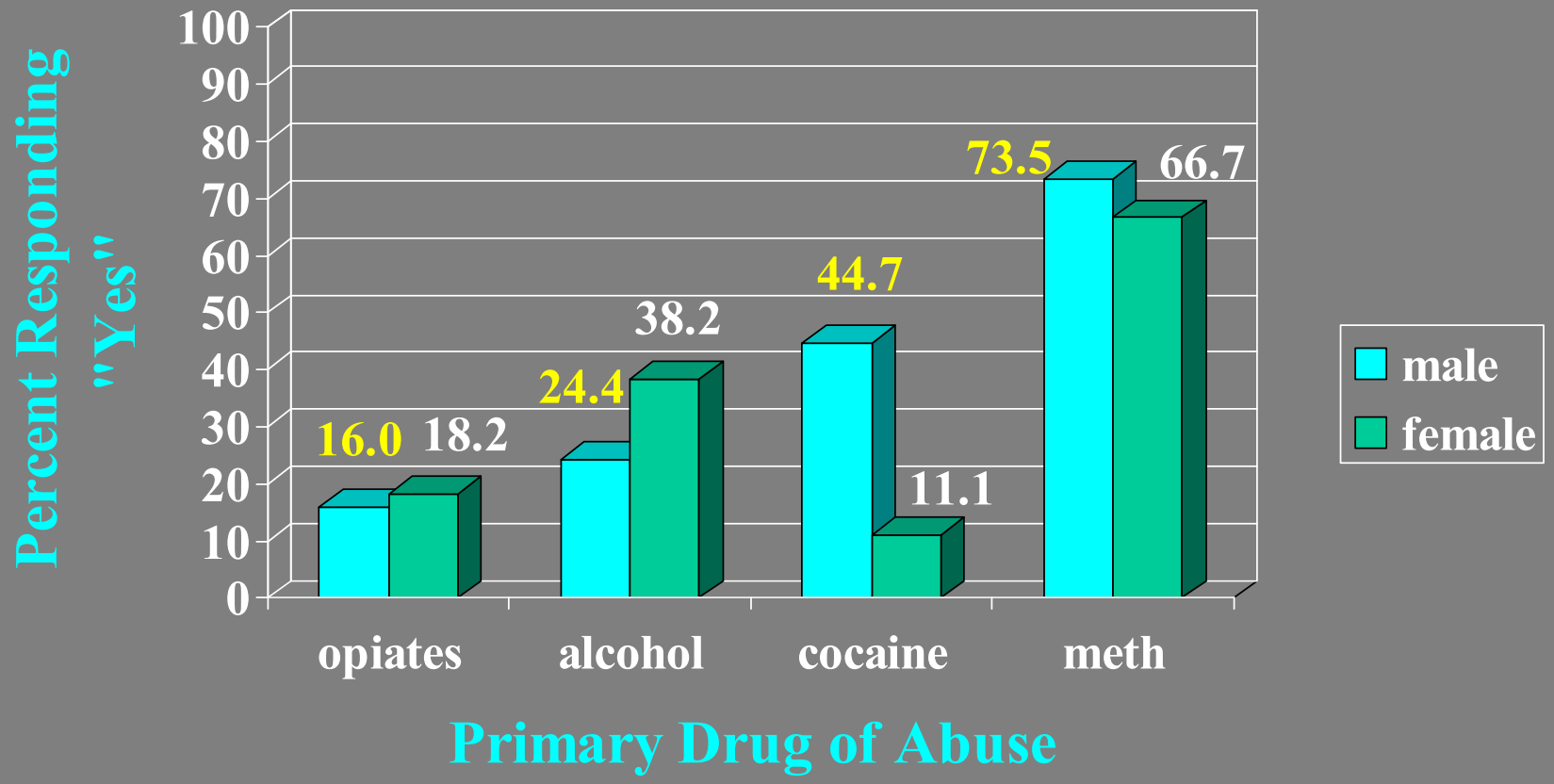
DECREASES

- Timidity
- Boredom
- Loneliness

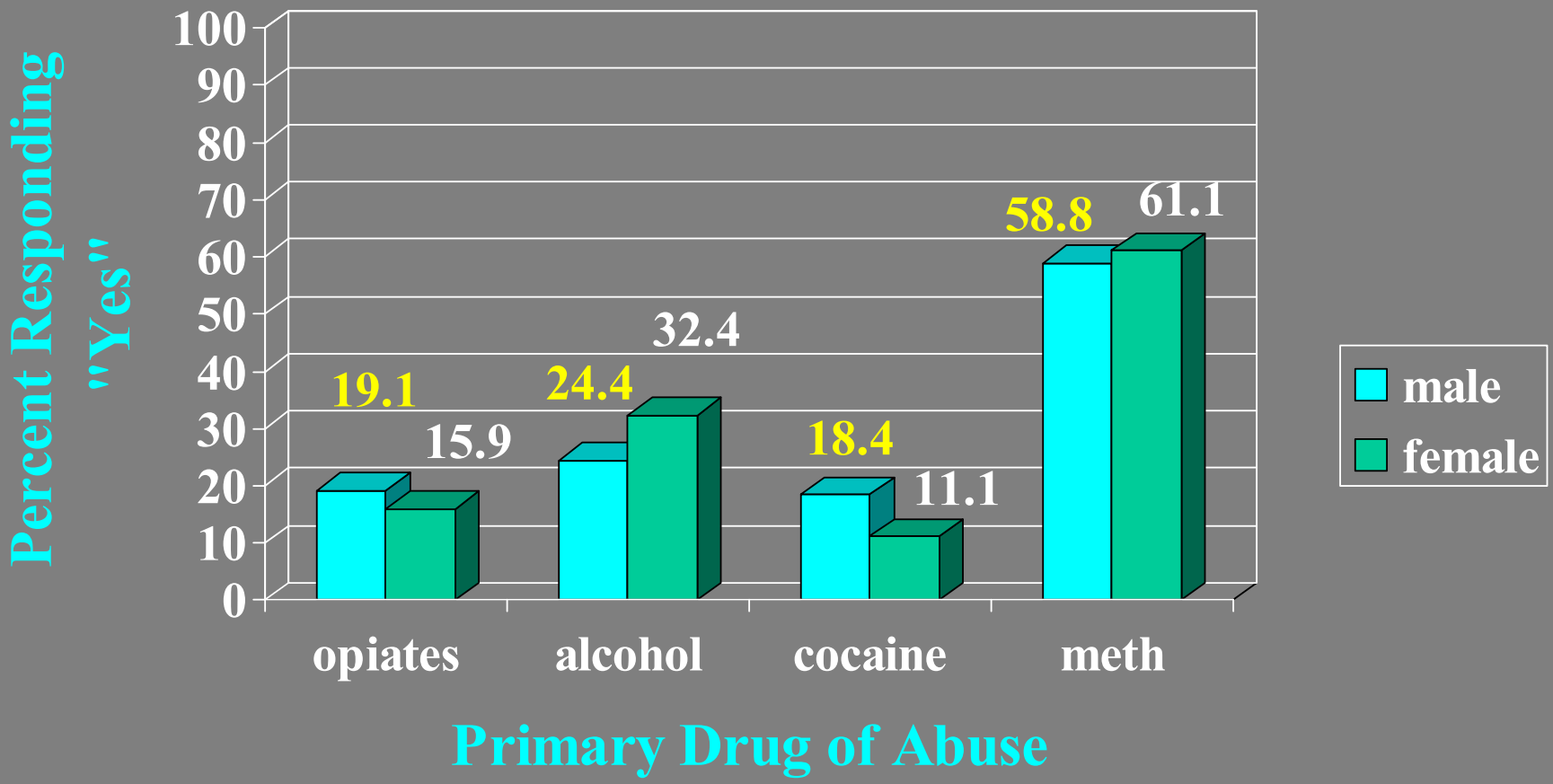
My sexual *drive* is increased by the use of …



My sexual *pleasure* is enhanced by the use of



My sexual *performance* is improved by the use of …



Macbeth, Act II Scene 2

McDuff asks Porter: ***"What 3 things does drink especially provoke?"***

Porter replies:

"Marry, sir nose-painting, sleep and urine. Lechery sir, it provokes and unprovokes; it provokes the desire, but it takes away the performance; therefore, much drink may be said to be an equivocator with Lechery: it makes him and it mars him; it sets him on and it takes him off; it persuades and disheartens him; makes him stand to and not stand to; in conclusion, it equivocates him in a sleep and giving him the lie, leaves him."

Methamphetamine – *Acute Toxic Effects*

- Acute chest pain, heart attack, or arrhythmia
- Stroke
- Seizures
- Delirium or confusion
- Trauma due to fighting or accident
- Paranoia
- Hallucinations
- Suicidal ideation
- Hyperthermia

So, what happens with chronic methamphetamine use?

After Methamphetamine Use

Normal

During Use

Elevated mood

After Use

Depression-like feelings, irritability

Methamphetamine – Chronic Physical Effects

ANOREXIA	**COUGH**	**HEADACHES**	**BRUXISM**
PULMONARY DISEASE	**DENTAL PROBLEMS**	**BURNED LIPS, SORE NOSE**	**SEPTAL PERFORATION**
DRY MOUTH	**WEAKNESS**	**SWEATING**	**TREMOR**
SINUS INFECTION	**OILY SKIN/ COMPLEXION**	**WEIGHT LOSS**	**IVDU COMPLICATIONS**

Methamphetamine – Chronic Physical Effects

Elevated Prolactin

- Swollen, tender breasts (men and women)
- galactorrhea
- amenorrhea
- infertility
- decreased libido

- Osteoporosis

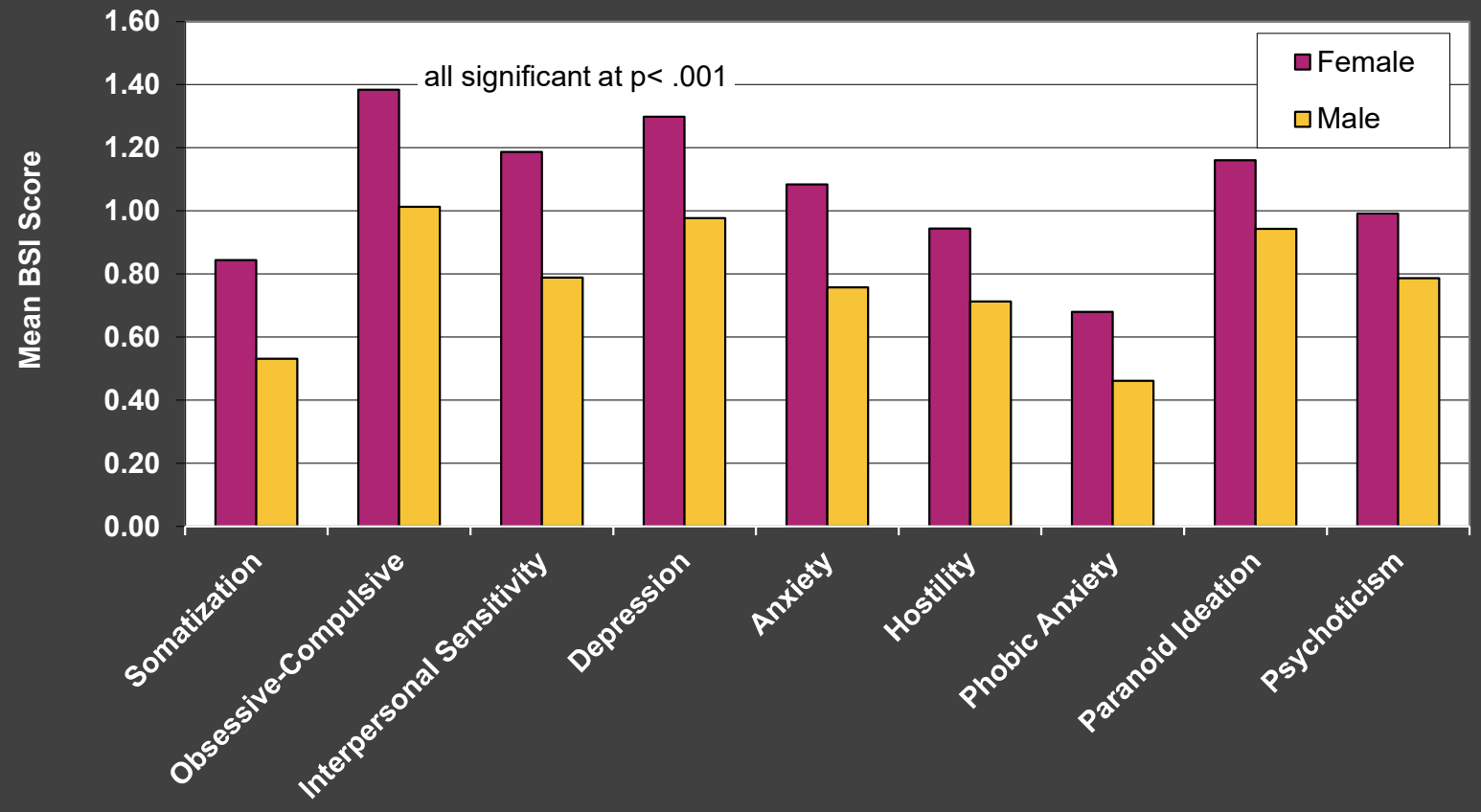
- Vasodilation
- Hypotension

- Chorea
- Dyskinesias
- Tics

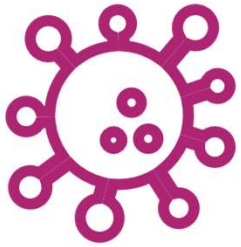
Methamphetamine – Chronic Psychological Effects

- **CONFUSION**
- **CONCENTRATION**
- **HALLUCINATIONS**
- **FATIGUE**
- **MEMORY LOSS**
- **INSOMNIA**
- **IRRITABILITY**
- **PARANOIA**
- **PANIC REACTIONS**
- **DEPRESSION**
- **ANGER**
- **PSYCHOSIS**

Behavior Symptom Inventory (BSI) Scores at Baseline on Admission



Other Neurotransmitters

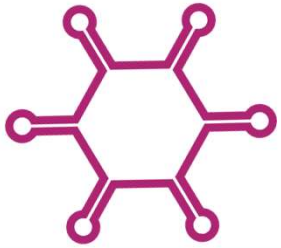


↓ Endogenous Opioid Activity

- No direct stimulant effect
- Cocaine indirectly ↓s

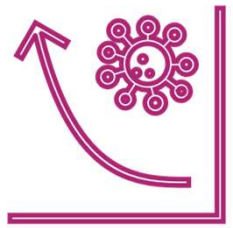
↓ Mesolimbic Glutamate

- Cocaine ↓s
- Amphetamine ↓s



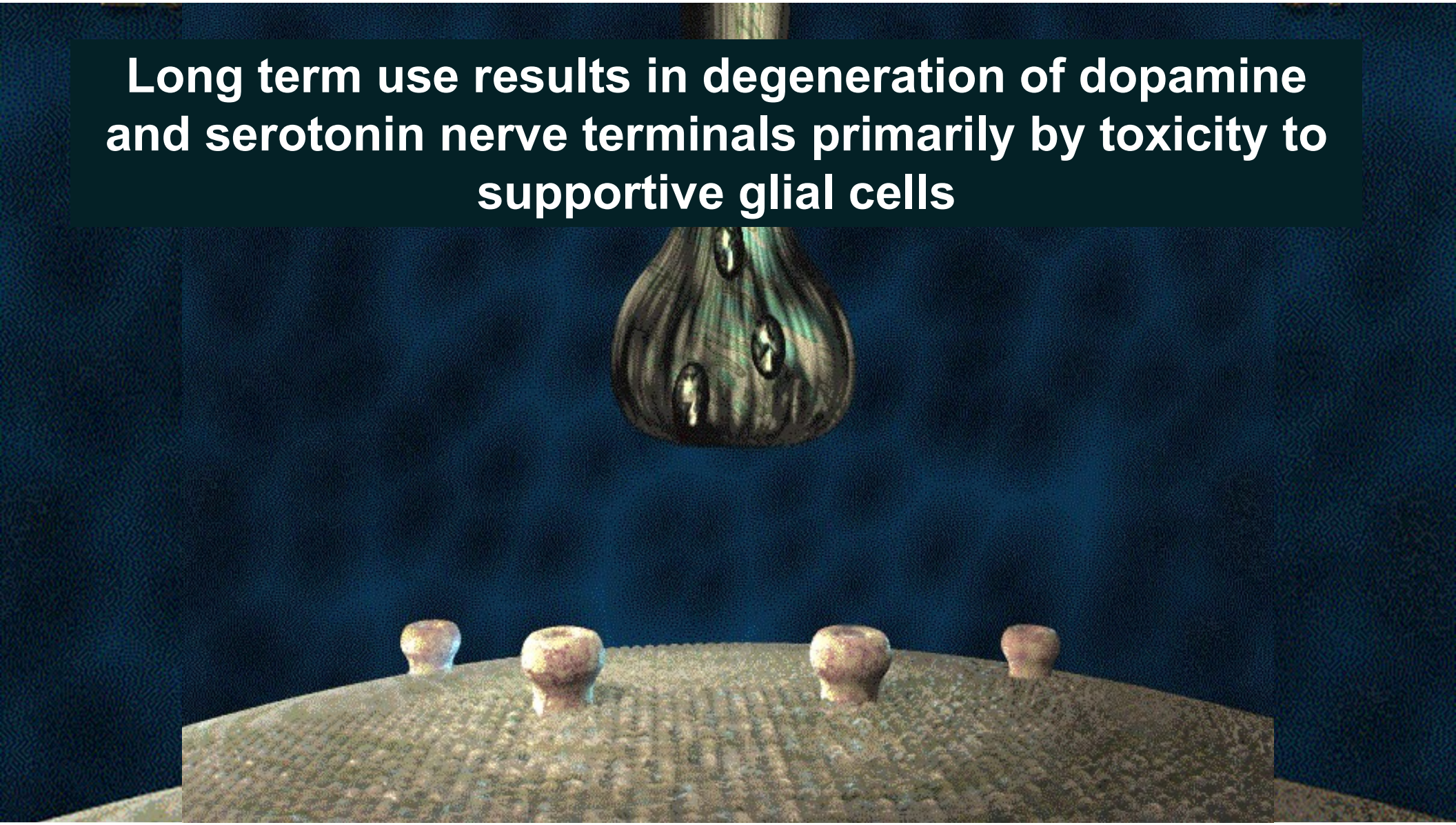
↓ Acetylcholine

- Cocaine ↓s



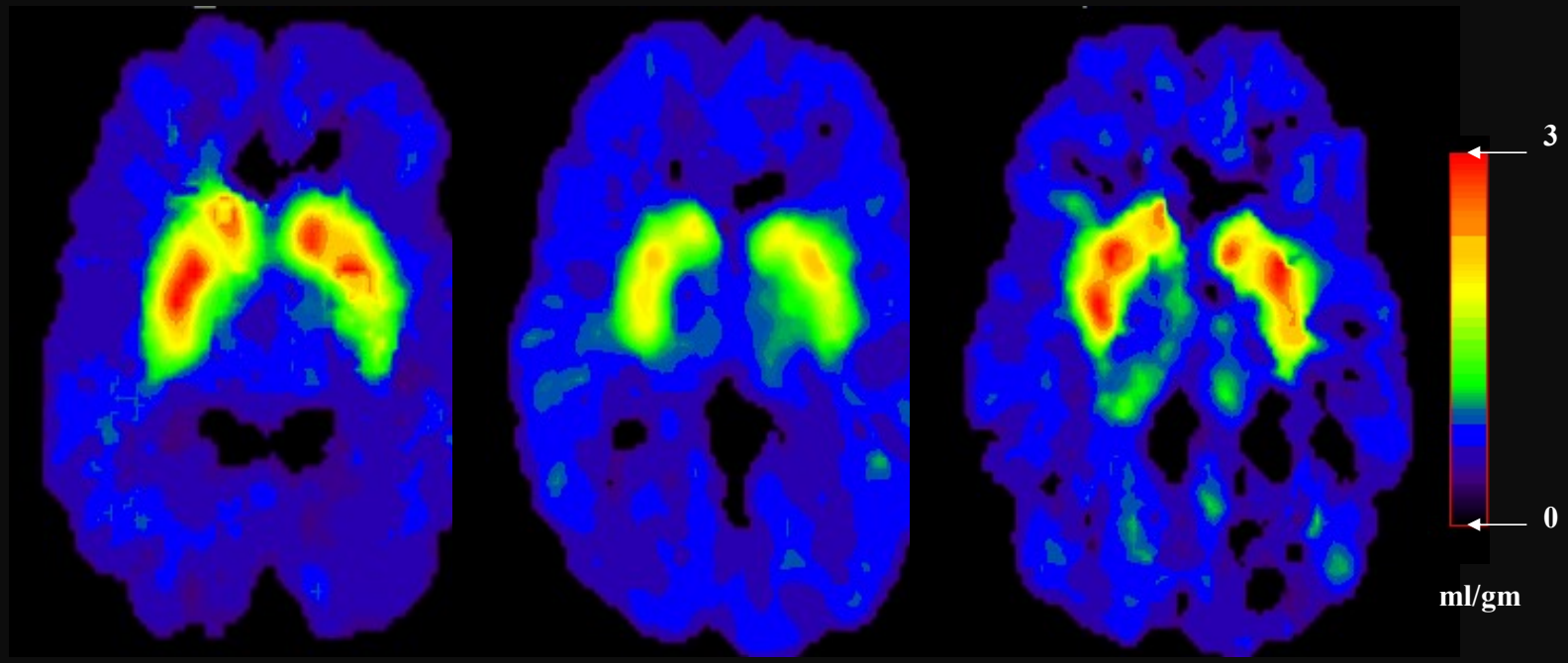
↓ Sodium Channel Blockage

- (cocaine only)


Long term use results in degeneration of dopamine and serotonin nerve terminals primarily by toxicity to supportive glial cells

Remember what that looks like on the inside in the brain?

Partial Recovery of Brain Dopamine Transporters in Methamphetamine (METH) Abuser After Protracted Abstinence



Normal Control | **METH Abuser** *(1 month detox)* | **METH Abuser** *(24 months detox)*

Source: Volkow, ND et al., Journal of Neuroscience 21, 9414-9418, 2001.

What's that look like on the outside of the brain?

Faces of Methamphetamine

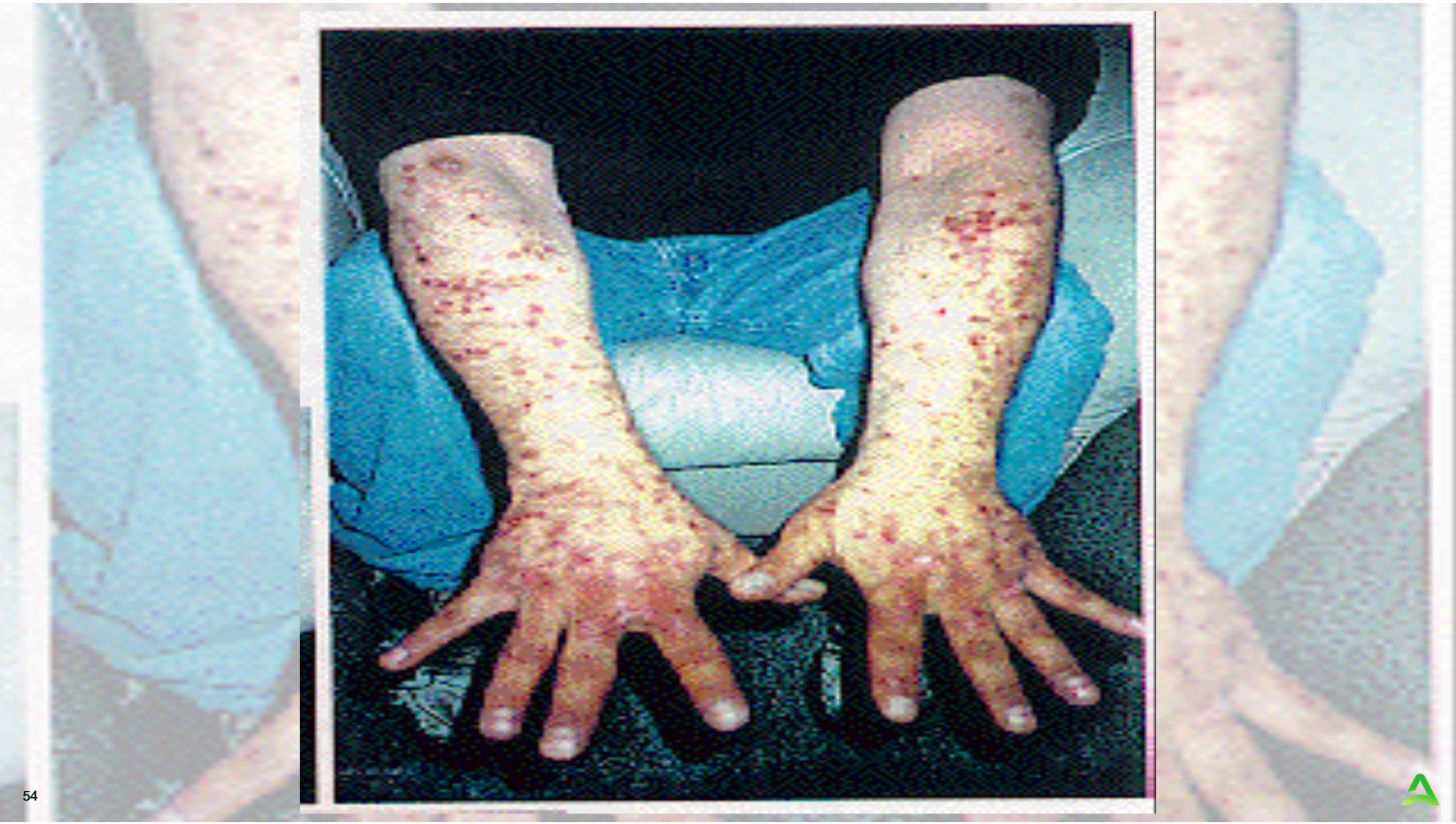
Images courtesy Multnomah County Sheriff's Office

Faces of Methamphetamine

Images courtesy Multnomah County Sheriff's Office

Faces of Methamphetamine

From the DEA's website http://www.usdoj.gov/dea/concern/concern.htm



METH Use Leads to Severe Tooth Decay

"METH Mouth"

Source: Richards, JR and Brofeldt, BT, J Periodontology, August 2000.

Medications

- Currently, there are *no* medications that can quickly and safely reverse life-threatening MA overdose; i.e., no antidotes.
- There are *no* medications that can reliably reduce paranoia and psychotic symptoms that contribute to episodes of dangerous and violent behavior associated with MA use.
- There are *no* medications that have been effective in significantly improving treatment

Psychosocial/Behavioral Treatments

NIDA has also produced several manuals that have been empirically tested with stimulant-using populations, including:

- Cognitive Behavioral Therapy (CBT)
- Contingency Management (CM)

CSAT Tip #33

A useful resource that presents a review of the existing knowledge about treatment effectiveness with stimulant users.

Treatments for stimulant dependence with empirical support

Motivational Interviewing

Cognitive Behavioral Therapy

12 Step Facilitation Therapy

Contingency Management

Community Reinforcement Therapy

Matrix Model developed at UCLA

Limitations on Current Treatments

Training and development of knowledgeable clinical personnel are essential elements to successfully address the challenges of treating MA users.

Training alone is insufficient if the funding necessary to deliver these treatment recommendations is not available.

Treatment funding policies that promote short duration or non-intensive outpatient services are inappropriate for providing adequate funding for MA users.

Special treatment consideration should be made for the following groups of individuals:

- Female MA users (higher rates of depression; very high rates of previous and present sexual and physical abuse; responsibilities for children).
- Injection MA users (very high rates of psychiatric symptoms; severe withdrawal syndromes; high rates of hepatitis, HIV).
- MA users who take MA daily or in very high doses.
- Homeless, chronically mentally ill and/or individuals with high levels of psychiatric symptoms at admission.
- Individuals under the age of 21.
- Gay men (at very high risk for HIV and hepatitis).

Contingency Management

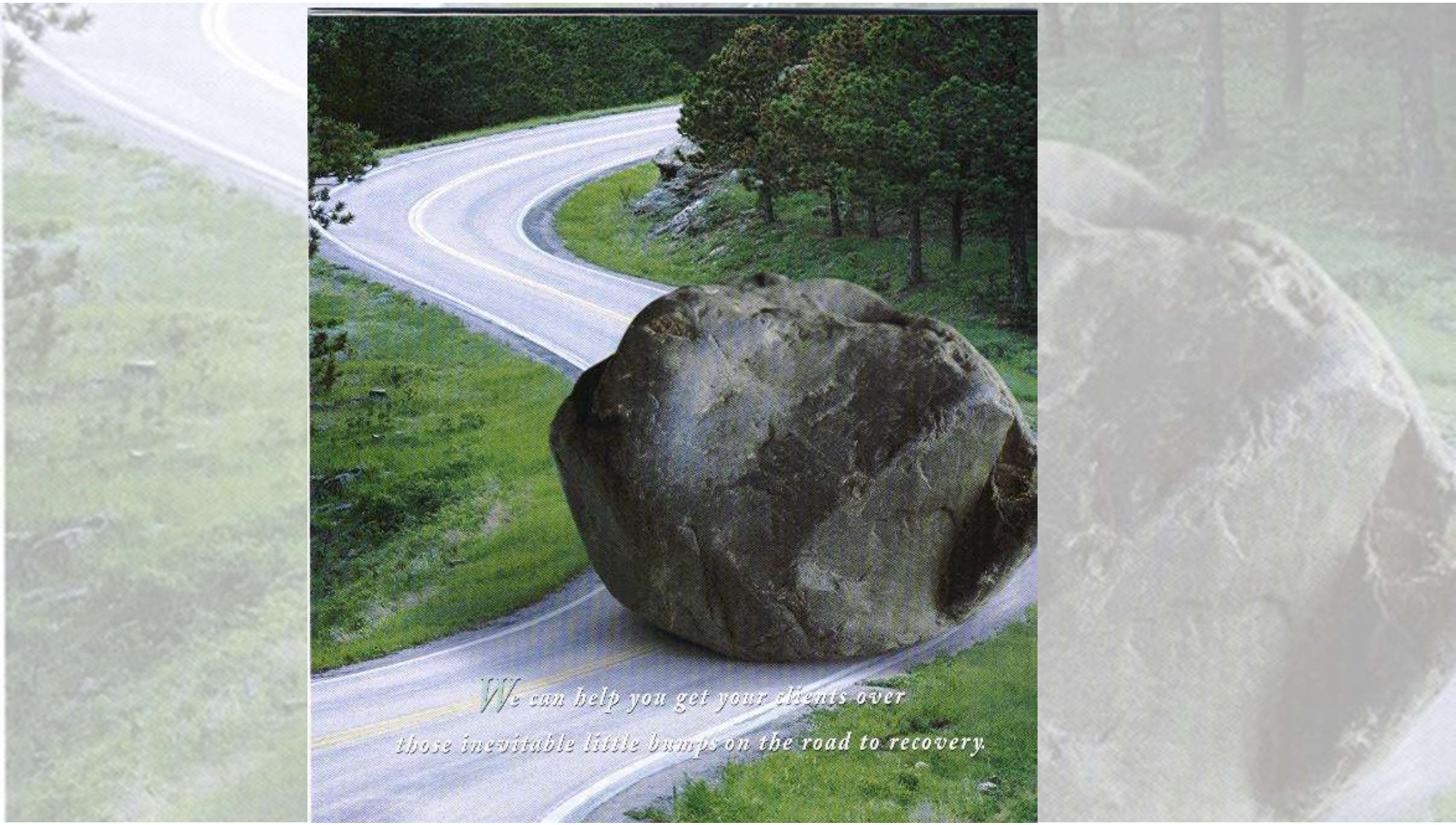
- Preliminary finding appear very positive.
- Powerful tool to improve engagement and retention and to reduce MA use

Matrix Model

Manualized, 16-week, non-residential, psychosocial approach used for the treatment of drug dependence.

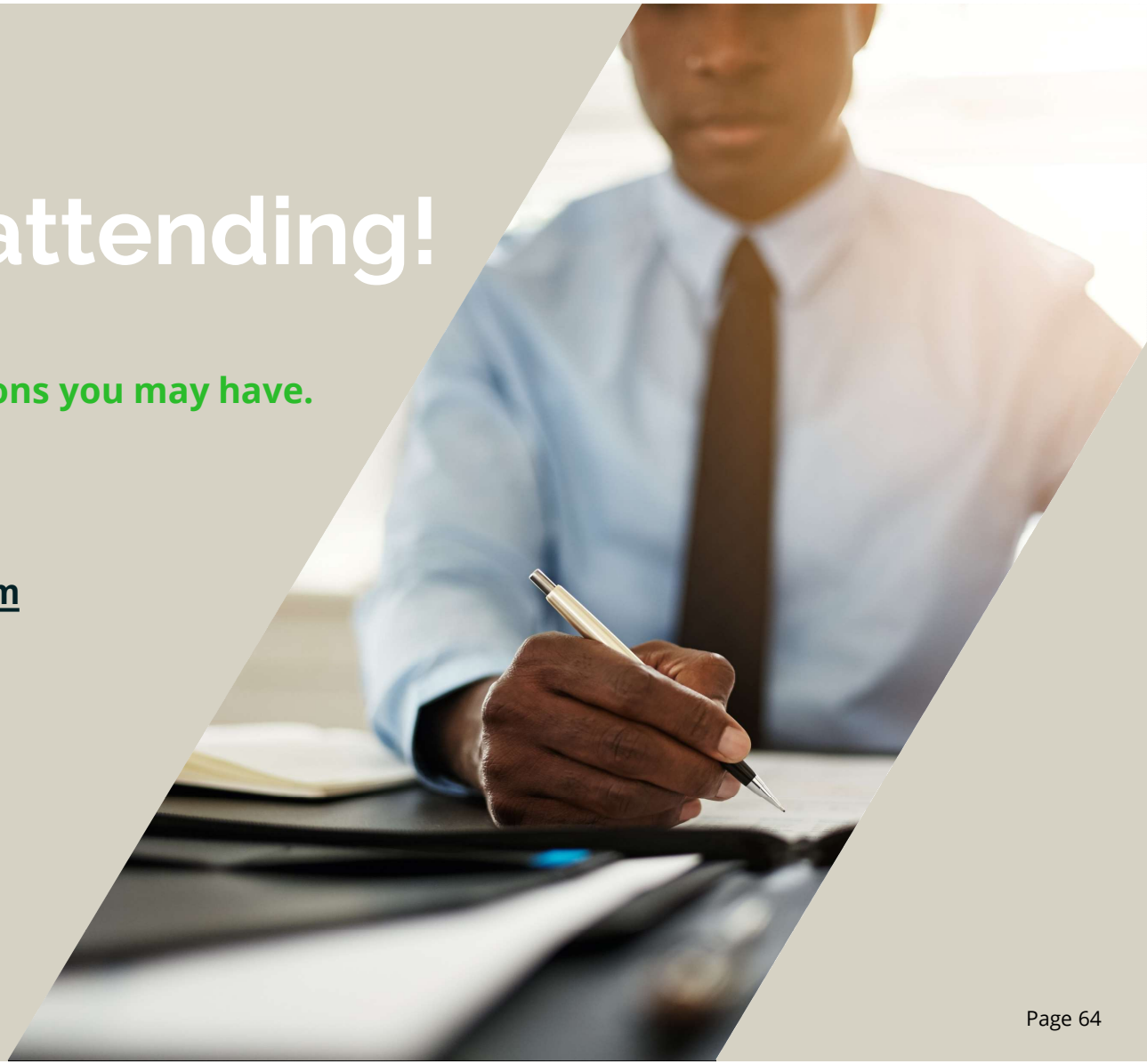
Designed to integrate several interventions into a comprehensive approach. Elements include:

- Individual counseling
- Cognitive behavioral therapy
- Motivational interviewing
- Family education groups
- Urine testing
- Participation in 12-step programs


We can help you get your clients over
those inevitable little bumps on the road to recovery.

Thank you for attending!

Please reach out with any questions you may have.



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