Developments in Addiction Treatment

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Abstract

Maintenance pharmacotherapy, replacement therapies, chemically assisted detoxification or recovery; agonist mediated "anti-priming" treatments, pharmacologic restoration of neuro-homeostasis, and "resetting" the brain with medication. Such terms would have been oxymoronic to the recovery field just a few short years ago. The historical evolution of "demand reduction" strategies is examined. Advances in understanding the neurobiology of addiction has resulted in an explosive growth in medications in development to provide detoxification and treatment for addictions. Newly approved medications for the treatment of specific drug addictions will be presented. Current issues of chemical dependency treatment as well as newer, more potent drug addictions of the 2000s will be discussed in detail during this presentation.

Goals: Participation will result in:

- ***Increased awareness of demand reduction policies developed by the ONDCP***
- ***Appreciation of the major issues involved in chemical dependency treatment***
- ***Understanding of medication strategies in development to treat addiction***
- ***Familiarity with the more potent abused drugs of the 2000's***
- ***Better comprehension of the new FDA approved medications for treatment of specific chemical dependencies***

Objectives: Upon completion participations will be able to:

- ✓ ***Describe the current ONDCP Demand Reduction strategy***
- ✓ ***List at least 4 major current issues of chemical dependency treatment***
- ✓ ***Name at least 5 FDA approved medications used to treat drug addictions***
- ✓ ***Identify at least 5 medication strategies in development to treat addiction***
- ✓ ***Explain and describe how marijuana, methamphetamine and heroin are all more potent and addictive in the 2000's as compared to the 1960's***
- ✓ ***Cite at least 3 examples of positive chemical dependency treatment outcomes that have been validated by rigorous outcome studies***

I. Policy Development by the ONDCP Drug Czars (Office of National Drug Control Policy)

1960's

Growing tolerance to marijuana abuse and resentment of harsh penalties.
Establishment of third major class of abused drugs – psychedelics: LSD and designer hallucinogen, entheogen, entactogen, deliriant, empathogen, psychotogen, psychotomimetogen, psycho-stimulant.
Explosion in youth abuse of drugs in US – we have never recovered from this.
Illicit manufacture of Crank and Crystal with speed epidemic by end of the 1960s.
Heroin and alcohol treatment were established. Both considered medical conditions but treatment of heroin was basically enforced cold turkey, white knuckle detox and alcohol was left up to either 12-Step or rigorous hospital treatment.
Barbiturate abuse was noted and treatment was only considered safe in hospital in-patient settings.
Abuse of drugs other than heroin, alcohol or barbiturates was deemed poly-drug abuse.
1960's ended with major methamphetamine epidemic that had no developed or suggested treatment.
Haight Ashbury Free Clinics opened 6/7/67 and immediately developed Hippocratic primum non nocere, symptomatic treatment approach of any drug addiction as well as the ARRRT talk-down intervention for "bad trips".

From 1930- 1962 Harry Anslinger (the first US Drug Czar) was commissioner of the Federal Bureau of Narcotics and focused his wrath on marijuana and people of color.
Richard Nixon creates SAODAP and names Dr. Jerome Jaffe (first official Drug Czar) its director.
Jaffe invested in Marie Nyswander and Vincent Dole to develop Methadone Treatment.
Le Dain Commission in Toronto 1960 concluded that youth marijuana abuse would be self-limiting to the generation of the Hippie. Jaffe used scare tactics and gateway or stepping stone arguments against the drug (Current research indicate that youth magnify the potential negative consequences of drug use but also grossly exaggerate potential benefits gained from using).

1970s

Enactment of Controlled Substance Abuse Act effectively stopped and limited methamphetamine abuse during this decade.
Marijuana use in US peaked in 1971 as did demand for more potent varieties brought about by sensimilla and other growing techniques.
Heroin abuse exploded with the deteriorating situation in Viet Nam and the Iran and South West Asia crisis for Jimmy Carter. Persian heroin changes the way heroin is trafficked and used in the US.
Quaalude abuse exploded across the nation and especially in SF Bay Area Asian and Pacific Islander communities.

A PCP epidemic snuck in and out during this decade since it was not included in most drug use surveys but it did created sensational headlines.

Free Base cocaine smoking developed in San Mateo, CA by the mid 1970s and Dr. Inaba testified to Congress in 1976 that the US will suffer a major Cocaine epidemic during the 1980s. At the time, scientist claimed cocaine to be psychologically but not physically addicting.

Residential treatment starts to develop into a major force of addiction treatment and some research begins on treatment of poly-drug addiction.

Haight Ashbury Free Clinics (HAFCI) develops Symptomatic, acupuncture and then Darvon N treatment for heroin addiction as an alternative for Methadone treatment. HAFCI also recognizes and begins dual diagnosis treatment.

The discovery of endorphin and enkephalins during the mid 1970 validates the science of addiction and addiction treatment.

President Nixon declared that drug abuse is America's number one enemy and initiates "War on Drugs on 6/17/71. Nixon then creates the DEA and the Office of Drug Abuse and Law Enforcement (ODALE) with Myles Ambrose to tackle Supply Reduction. He also appoints Dr. Robert Dupont director of National Institute on Drug Abuse (NIDA) and also head of Narcotics Treatment Administration to take charge of Demand Reduction. Despite Dr. Dupont's attack on methadone as enslavement of Black Americans, the Methadone Treatment Industry is established and is still the major treatment of opioid addiction in America.

Jimmy Carter elected in 1976 appoints Peter Bourne as Special Assistant to the President and Bourne first approached marijuana and cocaine as harmless but then endorsed Paraquat spraying. He resigned in two years under rumor of his own Quaalude abuse. Mathea Falco was Carter's International Narcotic Secretary and advocated for demand reduction while attacking supply reduction strategies.

In 1978, Congress amends the Comprehensive Drug Abuse Prevention and Control Act to allow asset forfeiture.

1980s

Cocaine abuse via "free base" known as "crack, rock or fry" explodes in US forcing acceptance of its addiction and development of cocaine or stimulant drug addiction treatment.

Designer Heroins (fentanyl and meperidine derivatives) cause death and Parkinson's disease.

Persian and other Southwest Asian heroins (Iran, Afghanistan, Iraq, Turkey, Pakistan) become more prevalent in the US and initiate an era of increasing street heroin potency.

Tar heroin from Mexico introduces a new form of this drug to the street. Tar from Columbia and even Africa soon follow.

HIV/AIDS contagion brings challenges to substance abuse treatment program.

Generation X and club drug abuse begins in Europe and quickly spreads to the US with Ecstasy (MDMA) being the drug of choice.

By 1989, methamphetamine abuse returns as dextro-isomer methamphetamine made from pseudoephedrine and ephedrine enables easy street manufacture of this more powerful amphetamine (3 to 4 times stronger than racemic d,l methamphetamine).
Increased recognition of adult children of addicts and family treatment issue.
HAFCI pioneers cultural relevance in treatment via Asian & Pacific Islander research initiatives. It also pioneers faith-based treatment initiatives at Glide Memorial, Allen Temple Baptist and McDonald Avenue Churches.
The science of addiction identifies the role of neurotransmitters in the process of addiction.

Ronald Reagan elected in 1980 and views addiction as a moral failure. To forward this attitude he creates the Office of Drug Control Policy by 1988 moving the Drug Czar's office into a cabinet position directly reporting to the president. He also passes the Anti-Drug Abuse Act in 1986 making penalties for Crack much harsher than for powder cocaine.
Carlton Turner was Reagan's first Drug Czar, claimed marijuana caused homosexuality and resigned after a few years after cornering the market on urine drug testing.
Robert Martinez was then appointed and is perhaps a composite role model along with Barry McCaffrey for Michael Douglas in the movie, Traffic. Martinez continues as Drug Czar into the Bush Sr. administration. In 1985, DEA agent Enrique Camarena was tortured and murdered in Mexico which created the phrase "narco-terrorism" and the policy of "zero tolerance" for drug abuse.
George H. Bush comes to office in 1989 and continues the Regan strategies. He sends troops into Panama and brings Manuel Noriega to trial for drug trafficking. Bush appoints William Bennett Drug Czar who attacks casual drug users as his zero tolerance strategy. Bennett also opposed rock and roll and multiculturalism.

1990s

Club drugs, Salvia divinorum as well as stronger marijuana and methamphetamine dominate most of this decade.
Medical developments in understanding and treating addiction lead to LAAM, naltrexone, and nicotine anti-priming approved treatments. Research into others includes a diverse range of approaches from amino acid and acupuncture to ibogaine and flumazemil (alleged to "reset" the brain).
Treatment's response to research scrutiny demonstrates great effectiveness and outcomes
Harm Reduction take root and shapes public treatment policies with support from powerful lobby groups like the Lindesmith Center
HAFCI promotes "treatment on demand" as the most effective harm reduction strategy and positive/motivational interventions in drug abuse treatment.
The science of addiction explodes during the "Decade of the Brain" via brain imaging and DNA technologies. It identifies the precise anatomy of compulsivity (meso-limbic reward reinforcement pathway) and craving is established as a medical consequence of addiction.

Bill Clinton comes into office in 1992 and appoints Dr. Lee Brown Drug Czar. Dr. Brown promotes community policing and parental responsibility but he concentrates on minorities and the poor in urban communities during Clinton's first presidential term.

General Barry McCaffrey is appointed Drug Czar during Clinton's second term. Gen. McCaffrey emphasizes military interdiction and zero tolerance like the Reagan and Bush strategies and initiates Plan Columbia. He also initiated inserting anti-drug propaganda into TV and movie scripts though he accepts that addiction is a disease.

2000s

Abuse of Club Drugs rapidly diminished after 911 and an explosive growth in prescription drug abuse among both youth and adults takes it place. Generation Xers become Generation Rxers as the abuse of Rx (prescription) opioids (Vicodan, Oxyconton), benzodiazepines & Soma, ADHD stimulants and even anabolic androgenic steroids increases. Even the abuse of non-prescription or OTC drugs like those containing dextromethorphan (DXM) increases along with diversion of Sudafed for methamphetamine manufacturing

Methamphetamine spreads eastward across America

Coerced Treatment is validated and advocated as states began to mandate treatment in lieu of incarceration of non-violent drug offenders

Varenicline, acamprosate, buprenorphine, bupropion and naltrexone are approved for addiction treatment and many other medications are in development for addiction treatment

The science of addiction identifies the role of the neo-cortex's orbito frontal cortex in addiction as a deficit of self-control with *f*MRI and "stop-signal test".

President George W. Bush appoints John Walters as Drug Czar in 2001. Walters believes that the Drug War has never been fought hard enough and also believes strongly in faith-based treatments. He regards criticism about harsh drug laws and racial disparities as a myth. Walters escalates General McCaffrey's Plan Columbia (US military involvement in Latin America) and cuts back on funding for treatment and education at home. He implements the President's National Drug Control Strategy in March 2004 which include three main strategies:

1. Federal funding to identify, catch, punish and expose drug experimentation by youth (<18) via drug testing in schools.
2. Federal payment vouchers that enable poor people to obtain recovery counseling especially at faith-based centers.
3. Combining efforts of the DEA, Dept. of Defense, Dept. of Homeland Security, and all Attorney General Offices to eradicate, interdict and disrupt the worldwide distribution of drugs. This includes the development of "fusion intelligence" (intelligence sharing between Departments) and the Counterdrug Technology Assessment Center to develop new resources to combat drug trafficking like better x-ray devices.

II. Current Issues in Treatment

The first decade of the second millennia has witnessed some major issues and challenges regarding better diagnosis and more effective treatment of chemically dependent individuals. These include: (1) expanding use of medications to aid in detoxification and recovery; (2) use of new imaging techniques to visualize anatomical or structural anomalies of the human brain that either result in or result from addiction; (3) development of more effective tools to diagnose addiction that can better match clients to specific treatment interventions (4) decreased but continued conflict between abstinence oriented recovery and harm reduction techniques; (5) increasing evidence that "coerced treatment" [e.g. Drug Courts] are as effective if not more effective in promoting positive long-term treatment outcomes as compared to voluntary treatment admissions; (6) increased emphasis on evidence-based best practices in treatment with decreased appreciation of practice-based clinical management (7) continued deplorable lack of resources to provide sufficient treatment (that has been proven to work according to outcome studies).

III. Research Validated Diagnostic Tools include the following:

ASI (Addiction or Alcohol Severity Index) = Six area of physical or behavioral functioning affected by substance use/abuse are assessed through 200 items. Also **ASI-Lite** a shortened version of the ASI with 22 less questions and **T-ASI** modified for assessment of teen drug use

AUDIT = 10 item screen: frequency, daily amount, incidents of 6 or more drinks, inability to stop, inability to fulfill normal expectations, eye opener, guilt/remorse, black/brown-outs, suffered or injured someone while drinking, others suggest moderating your drinking. Score of 8 or more indicates hazardous drinking

B-MAST = 10 item brief screen assessment of the Michigan Alcoholism Screening Test: Alcohol/Drugs – **MAST/AD** (25 yes/no questions) & **M-SAPS =** Substance Abuse Problem Scale; **SMAST-G** = Short MAST for Geriatrics

CAGE = Cut down failures, Angered about discussing drinking, Guilt or shame about use, and need for morning Eye opener to function

CRAFFT – driving a Car while high, use to Relax, use Alone, Forget things while high, Family and/or friends ask you to cut down, gotten into Trouble while on alcohol or drugs

DSM IV-TR (Diagnostic and Statistical Manual of mental disorders) = delineates substance use from substance induced disorders. Use is divided into substance abuse and dependence with descriptions of negative impact on social/occupational functioning to determine abuse and pathological effects of tolerance or withdrawal symptoms to confirm dependence

MODCRIT (Modified CRIT) = 35 item structured interview questions a shortened version of the National Council on Alcoholism's **CRIT** (CRITeria for the diagnosis of alcoholism) evaluate two domains: physical/clinical parameters and behavioral/psychological/attitudinal impact

RAPS4 (Rapid Alcohol Assessment Screen) = 4 items: guilt, blackouts, failing normal expectations, eye opener

SAAST (Self-Administered Alcoholism Screening Test) = 35 yes/no questions

SSA (Selective Severity Assessment = 11 physiologic signs (e.g. pulse, temperature, tremors) are assessed to confirm severity of addiction

T-ACE = Tolerance, Annoyed, Cut Down, Eye Opener

TWEAK = Tolerance (just begin to feel drug effects after 3 or more drinks or hits, able to hold 6 or more drinks or hits)=2, Worried=2, Eye Opener=1, Amnesia=1, Kut Down=1: Score of 3 or more indicates problem

DAST= Drug Abuse Screening Test, a five minute, 20-item scale that can be used for screening, treatment planning and post-treatment outcome evaluation. The DAST assesses the consequences of drug use and has been validated against the DSM-III diagnostic criteria

PESQ = Targeted for adolescents, the Personal Experience Questionnaire has 18 questions , takes 25 minutes and screens for both drugs and alcohol. Specifically, it examines problem onset, psychological and social functioning, problem severity and frequency of use, and can detect "faking"

4P's Plus = This was developed by Dr. Ira Chasnoff of the Children's Research Triangle, Chicago, Illinois. It is being proffered as a universal pre-screening tool of all pregnancies for potential alcohol/nicotine, substance abuse and domestic violence problems. The P-questions evaluate **P**arental history of alcohol or drug problems; **P**artner's use of alcohol or drugs; **P**ast personal history of alcohol use; and use of either tobacco or alcohol during the month preceding **P**regnancy (also validated for 28 days after delivery). Any use of tobacco or alcohol 30 days before pregnancy or within 28 days after delivery indicates the need for further assessment or intervention.

ASAM PPC-2R = American Society of Addiction Medicine Patient Placement Criteria Revised to address co-occurring disorders, adolescent criteria, and residential levels of care clarification evaluates six dimensions of illness severity (acute intoxication/withdrawal potential; biomedical conditions and complications; emotional, behavioral or cognitive conditions and complications; readiness to change; relapse, continued use or continued problem potential; and recovery environment). These match patients to five levels of care (0.5-Early Intervention; I-Outpatient Treatment; II-Intensive Outpatient/Partial Hospitalization; III-Residential/Inpatient Treatment and; IV-Medically-Managed Intensive Inpatient Treatment). These have been expanded to include nine treatment sub-levels for each Level I-IV expressing gradations of treatment intensity within those existing levels of care. As patients progress in their recovery treatment efforts, the assessment can be revisited and redone to move them into different levels of services that match their current needs.

IV. Evidenced Based Best Prevention and Treatment Practices

SAMHSA has created an inventory of their recommended prevention and treatment interventions known as the National Registry of Evidenced-based Programs and Practices (NREPP). This registry can be accessed at www.modelprograms.samhsa.gov Over 160 programs are currently described and listed as either model, effective or promising

programs at this site. In the spring of 2006, the NREPP was expanded and revised to include treatment of mental health as well as addictive disorders.

Based upon a large number of research projects over the past several years, SAMHSA also developed a 13-point guide for effective treatment of addiction known as the Principles of Drug addiction treatment:

1. **No single treatment is appropriate for all individuals.** Matching treatment settings, interventions, and services to each individual's particular problems and needs is critical to his or her ultimate success in returning to productive functioning in the family, workplace, and society.
2. **Treatment needs to be readily available.** Because individuals who are addicted to drugs may be uncertain about entering treatment, taking advantage of opportunities when they are ready for treatment is crucial. Potential treatment applicants can be lost if treatment is not immediately available or is not readily accessible.
3. **Effective treatment attends to multiple needs of the individual, not just his or her drug use.** To be effective, treatment must address the individual's drug use and any associated medical, psychological, social, vocational, and legal problems.
4. **An individual's treatment and services plan must be assessed continually and modified as necessary to ensure that the plan meets the person's changing needs.** A patient may require varying combinations of services and treatment components during the course of treatment and recovery. In addition to counseling or psychotherapy, a patient at times may require medication, other medical services, family therapy, parenting instruction, vocational rehabilitation, and social and legal services. It is critical that the treatment approach be appropriate to the individual's age, gender, ethnicity, and culture.
5. **Remaining in treatment for an adequate period of time is critical for treatment effectiveness.** The appropriate duration for an individual depends on his or her problems and needs. Research indicates that for most patients, the threshold of significant improvement is reached at about 3 months in treatment. After this threshold is reached, additional treatment can produce further progress toward recovery. Because people often leave treatment prematurely, programs should include strategies to engage and keep patients in treatment.
6. **Counseling (individual and/or group) and other behavioral therapies are critical components of effective treatment for addiction.** In therapy, patients address issues of motivation, build skills to resist drug use, replace drug-using activities with constructive and rewarding nondrug-using activities, and improve problem-solving abilities. Behavioral therapy also facilitates interpersonal relationships and the individual's ability to function in the family and community.
7. **Medications are an important element of treatment for many patients, especially when combined with counseling and other behavioral therapies.** Methadone and levo-alpha-acetylmethadol (LAAM) are very effective in helping individuals addicted to heroin or other opiates stabilize their lives and reduce their illicit drug use. Naltrexone is also an effective medication for some opiate addicts and some patients with co-occurring alcohol dependence. For persons addicted to nicotine, a nicotine replacement product (such as patches or gum) or an oral medication (such as bupropion) can be an effective component of treatment. For patients with mental disorders, both behavioral treatments and medications can be critically important.
8. **Addicted or drug-abusing individuals with coexisting mental disorders should have both disorders treated in an integrated way.** Because addictive disorders and mental disorders often occur in the same individual, patients presenting for either condition should be assessed and treated for the co-occurrence of the other type of disorder.
9. **Medical detoxification is only the first stage of addiction treatment and by itself does little to change long-term drug use.** Medical detoxification safely manages the acute physical symptoms of withdrawal associated with stopping drug use. While detoxification alone is rarely sufficient to help addicts achieve long-term abstinence, for some individuals it is a strongly indicated precursor to effective drug addiction treatment.

10. **Treatment does not need to be voluntary to be effective.** Strong motivation can facilitate the treatment process. Sanctions or enticements in the family, employment setting, or criminal justice system can increase significantly both treatment entry and retention rates and the success of drug treatment interventions.

11. **Possible drug use during treatment must be monitored continuously**. Lapses to drug use can occur during treatment. The objective monitoring of a patient's drug and alcohol use during treatment, such as through urinalysis or other tests, can help the patient withstand urges to use drugs. Such monitoring also can provide early evidence of drug use so that the individual's treatment plan can be adjusted. Feedback to patients who test positive for illicit drug use is an important element of monitoring.

12. **Treatment programs should provide assessment for HIV/AIDS, hepatitis B and C, tuberculosis and other infectious diseases, and counseling to help patients modify or change behaviors that place themselves or others at risk of infection.** Counseling can help patients avoid high-risk behavior. Counseling can also help people who are already infected manage their illness.

13. **Recovery from drug addiction can be a long-term process and frequently requires multiple episodes of treatment.** As with other chronic illnesses, relapses to drug use can occur during or after successful treatment episodes. Addicted individuals may require prolonged treatment and multiple episodes of treatment to achieve long-term abstinence and fully restored functioning. Participation in self-help support programs during and following treatment often is helpful in maintaining abstinence.

V. Increasing Interest in the use of Treatment Workbooks or Manuals

Interest in workbooks or manuals to provide education, evaluation and even self-administered counseling to substance abusers has grown out of the evidences based best practices movement. Some NREPP registered treatment interventions (e.g. MATRIX for stimulant abuse) first used such resources during research process to ensure that treatment outcomes from their protocols were not influenced by particular styles or personalities of individual substance abuse counselors. Analysis of outcome data first validated the efficacy of the intervention and then went on to demonstrate that better outcomes resulted from the use of workbooks or manuals than from individual and/or group counseling without the use of such resources. Recovery workbooks provide better structure to the recovery process, they are often completed by clients during their own time – they're practical and empowering, help to identify areas of clinical need for counselors or programs, provide continual resources for counselor interactions, lessen guilt and shame of sharing negative or painful thoughts and experience with others, and empower clients while instilling self-efficacy for them to make the desired changes in their lives.
Examples of recovery workbooks: The Forgotten Five Steps - www.recoverforever.com
Holistic Health Recovery Program Workbook – info.med.yale.edu/paych/3s/hhrp_wkbk.html
Integrated Dual Disorders Treatment Workbook – www.addictioninfo.org/content/articles/892/1/integrated-dual-disorders-treatment-workbook/introduction.html

VI. FDA Approved Medications for Addiction Treatment

For Alcohol Dependence
***Disulfiram* (Antabuse®)** was approved in 1948 and is one of the oldest medications approved to specifically treat an addiction. It modifies the liver metabolism of alcohol

resulting in a toxic build up of acetaldehyde when alcohol is drunk. Aversive consequences (flushing, nausea, vomiting, dizziness, rapid heart beat) occur immediately thus discouraging further use of alcohol in the recovering alcoholic. "Coerced Treatment" (criminal justice system imposed) is creating a bit of a "come-back" for this medication as compliance to taking the medication is increased. Disulfiram is also being looked at as a treatment for cocaine and other stimulants addressed later.

Naltrexone **(ReVia® & Vivitrol®)** was first approved in 1984 by the FDA to treat opiate addiction. In December 1994 naltrexone was approved to treat alcohol craving, a new indication for use of the medication. Precisely how naltrexone decreases cravings for alcohol is unknown. The drug blocks opiates from acting in the brain; this includes the brain's own naturally occurring opioid neurotransmitters, endorphins. Some speculate that this disrupts activation of the reward reinforcement circuitry of brain to curb craving.

Acamprosate **(Campral®)** was approved to treat craving in alcoholism in July 2004. It had been used effectively in Europe for this indication since 1989. Its mechanism of action is unknown but it modulates the GABA type A&B receptors as well as the NMDA glutamate receptor which are all disrupted by alcohol consumption. Acamprosate is thought to stabilize these receptors to moderate the craving response. Though studies prior to its approval and long prior history of effective use in Europe indicated significant effectiveness to decrease alcohol craving, post FDA approval studies have shown it to be less effective than either naltrexone or disulfiram in preventing slips and relapses.

Naltrexone injectable suspension **(Vivitrol®)** received FDA approval on 12/28/05. Though naltrexone had already received approval to treat alcohol craving in 1984, this is a new formulation of the medication that permits its use by monthly injection to ensure that the medication is not being neglected and therefore reduces patient compliance problems. Recovering alcoholics taking the oral ReVia® form of this medication often discontinued its use on their own after a few months which often resulted in a relapse.

For Nicotine Addiction

Varenicline **(Chantix®)** was approved on May 20, 2006 to treat tobacco addiction. It is a nicotine receptor antagonist that also slows the release of dopamine which decreases nicotine craving.

Bupropion or ***amfebutamone*** **(Zyban® , Wellbutrin®)** was approved by the FDA in December of 1996 as the first oral pill to treat nicotine craving. This medication is a dopamine and norepinephrine reuptake inhibitor but its precise mechanism of decreasing cravings for nicotine is not yet known.

Nicotine replacement therapy: nicotine gum by prescription was approved in 1984 while later, in 1996, **Nicorette®** gum was approved for non-prescription availability. From 1991 to 1992, four transdermal patch delivery systems for nicotine were approved two of which (Nicotrol® and Nicoderm CQ®) became non-prescription products by 1996 and the other two (ProStep® and Habitrol®) by 1999. By November 2002, nicotine was also available for tobacco cessation treatment via nasal spray (1996), inhaler (1998), and lozenges (2002). Nicotine replacement therapy is used to substitute for more harmful tobacco smoking as well as a form of addiction treatment called anti-priming therapy.

For Opiate/Opioid Addiction

***Buprenorphine* (Suboxone® Subutex®)** was approved in October 2002 for opioid detoxification and replacement therapy. Suboxone combines naloxone with buprenorphine to prevent injection misuse of the medication. It is a powerful partial opioid receptor agonist at low to moderate doses but soon reaches a "ceiling effect when dosages are increased and then becomes an opioid antagonist at high dose. Physicians are granted special DEA permission to use this medication for opioid addiction at their offices rather than having to be part of an approved treatment clinic. This practice is known as Office Based Opioid Addiction Treatment or "OBOAT".

***Naltrexone* (ReVia®, Trexan®)** was approved by the FDA in 1984 to treat opioid dependence. It is an opioid receptor antagonist that blocks the actions all opioids. This means that even if a heroin addict slips and injects heroin or if they use any other opioid drug, they will have no reaction to it while they are on naltrexone. It has also been found to decrease craving and is used to prevent relapses.

***LAAM or levo-alpha-acetyl-methadol* (Orlaam®)** was approved as a replacement therapy for opioid addiction in July 1993. It is longer acting than methadone and could therefore be dosed trice-weekly instead of daily. It was said to also be potentially less euphoric and thus less prone to be abused with milder withdrawal symptoms than methadone. The manufacturer of LAAM, Roxanne pharmaceuticals voluntarily ceased production of the medication in 2003 due to concerns that it caused cardiac arrhythmias and LAAM is no longer available in the U.S.

***Methadone* (Dolophine®, Methadose®, Tussol®, Adanon®)** was approved during the mid to late 1960s as detoxification and replacement therapy for heroin addiction. Methadone remains the standard medication used to treat opioid dependence. Since it is orally acting and has a long duration of action (prevents withdrawal symptoms for 24 hours or longer), it is a successful harm reduction strategy with close to 50 years of research demonstrating its ability to reduce medical and legal complications of opioid addiction.

For Stimulant Drug Addiction

There are no medications that are FDA approved for the specific indication of treating methamphetamine or cocaine dependence. However, many FDA approved medications are being used to treat the symptoms associated with stimulant addiction withdrawal and several drugs are in IND development to treat this condition. Abuse of stimulant drugs disrupt the same brain neurotransmitters that are imbalanced in depression and thought disorders so antidepressant (e.g. *sertraline, trazodone, imipramine*) and neuroleptic (e.g. *haloperidol, respiridon, olanzapine*) medications are frequently used to treat withdrawal symptoms from stimulants. Dopaminergic medications (*L-dopa, amantidine, bromocriptine*) have also been used to dampen cravings for stimulant drugs.

For Sedative-Hypnotic Dependence

Addiction to barbiturates, benzodiazepines, other sedative-hypnotics, muscle relaxants, some inhalants, and even alcohol can result in fatal seizure activity during their withdrawal and must therefore be medically managed. Though no medications have been FDA approved to specifically treat this condition, many drugs approved to treat seizure disorders (phenobarbital, various benzodiazepines, phenytoin, carbamazepine, gabapentin) are currently used effectively to treat sedative-hypnotic drug dependence. A

benzodiazepine antagonist, flumazemil (Mazicon®, Ro-Mazicon®) approved by the FDA for overdose treatment may be of benefit in the treatment of alcohol, benzodiazepine, and other depressant drug addictions."

VII. Medication & Protocol Development Strategies for Addiction Treatment

Detoxification: Medications that moderate or eliminate the withdrawal syndrome in addicts have been shown to be effective in engaging them into long-term treatment. Some examples of this detoxification development include clonidine and lofexidine to treat opioid withdrawal; selegiline, propranolol (a beta blocker), and SSRI antidepressants (paroxetine) for cocaine and stimulant addiction; and phenobarbital or lorazepam for alcohol or sedative-hypnotic dependence (O'Brien, 1997; Vocci, 1999).

Rapid Opioid Detoxification - This strategy uses various medications to manage opioid withdrawal symptoms in combination with naloxone or naltrexone, opioid antagonists that force the rapid onset of the abstinence syndrome. Opioid addicts suffer little symptoms and are quickly able to return to their daily lives without suffering prolonged withdrawal. Medications used to alleviate the naloxone/naltrexone forced onset of opioid withdrawal consist of:

- clonidine, a medication that dampens brain hyperactivity associated with withdrawal. Physical detoxification from opioid tissue dependence is accomplished within 2–3 days.
- midazolam, a benzodiazepine sedative that is said to accomplish opioid detoxification in 24 hours.
- lorazepam or midazolam combined with clonidine is used while an addict is anesthetized with propofol. Detoxification of an opioid addict is alleged to occur within only 6–8 hours.

These methods of rapid detoxification are medically dangerous and require intensive medical supervision. Further it is very important to remember that the techniques only accomplish physical detoxification and do not address the long-term behavioral and emotional components of addiction (Lorenzi et al., 1999; Cucchia et al., 1998; Byrne, 1998; Dyer, 1998; Barter et al., 1996; Senft, 1991).

Replacement or Agonist Effects - Controversy over whether this type of therapy is more harm reduction than recovery remains very heated in the addiction treatment community. However, few can deny the effectiveness of methadone replacement therapy in producing positive benefits for both the addict (reduced morbidity and mortality while increasing overall life functioning) and for society (cost effectiveness and reduction in crime) (Ball & Ross, 1991). Positive results from methadone maintenance have stimulated the search for other replacement or agonist therapies. Methylphenidate and pemoline for cocaine and stimulant dependence and SSRI antidepressants and GHB (gamma hydroxybutyrate) for alcohol and sedative-hypnotic addiction are examples of replacement therapies in development to treat addictive disorders (O'Brien, 1997; Vocci, 1999). Propoxyphene and tramadol as opioid replacement therapies have also been investigated.

Antagonist (blocking) Medications or Vaccines - Medications or vaccines that block the effects of addictive drugs without inducing their own major psychoactive effects are widely accepted as recovery-oriented treatment approaches. While on these types of agents, addicts will be unable to experience the effects of an abused drug should they have a slip. This destroys the addict's motivation for using and promotes continued abstinence. Significant examples of this treatment approach are the development of depo-naltrexone for opioid addiction and UH-232 or NGB-2904 for cocaine addiction. A cocaine vaccine, TA-CD, that produces antibodies for cocaine, as well as two vaccines for nicotine - CYT-002-NicQb (Nicotine-Qbeta) and NicVax - prevents these drugs from acting in the brain, are also in development (O'Brien, 1997; Vocci, 1999; Carrera et al., 1996; Fox et al., 1996; Xi, et al. 2006; Heading CE, Drug evaluation: CYT-002-NicQb, a therapeutic vaccine for the treatment of nicotine addiction, Curr Opin Investig Drugs, 8(1):71-7, Jan. 2007; Smokers invited to test vaccine against nicotine addiction. Press Release, University of California – San Francisco, June 9, 2006). An alcohol/benzodiazepine antagonist imidazobenzodiazepine or Ro 15-4513 researched over 20 years ago is again in investigation as a treatment for alcohol or benzodiazepine addiction (Wallner, Hanchar & Olsen, 2006).

Mixed Agonist-Antagonist - A single medication can have an agonist effect at one receptor site and an antagonist effect at another site. Or a combination of drugs are used together that work independently at different receptor sites to accomplish the same overall agonist-antagonist goal. The agonist component of this approach is targeted to prevent withdrawal while the antagonist effects prevent craving by blocking any further drug use. Examples of this approach are the developments of butorphanol for opioid addiction; cyclazocine in cocaine dependence; and the combination of low-dose nicotine with mecamylamine to treat nicotine addiction. Rapid opioid detoxification described previously also employs this technique of combining agonist with antagonist medication to treat heroin and other opioid addictions (O'Brien, 1997; Rose, Behm, Westman, et al., 1994).

Anti-craving & Anti-cued Craving - Craving or drug hunger is now an established component of addiction. Negative emotional states (e.g., hungry, angry, lonely, tired—HALT; and restless, irritable, discontent—RID) as well as imbalances in brain chemistry due to drug use cause endogenous craving. Environmental cues or triggers (e.g., drug odors, white powders, paraphernalia, crack houses, drug-using acquaintances) also induce a great potential for relapse. Medications that can check or curb the endogenous craving and/or environmental cued-craving responses have witnessed dramatic development in treating addictions (O'Brien, 1977). Naltrexone has been fully approved as an anti-craving treatment for alcoholism and is in development to see if it also blocks cocaine and opioid craving (O'Brien, 1997; Volpicelli, O'Brien, Atterman, & Hayashida, 1992; O'Malley et al., 1992). A concern regarding potential liver toxicity with naltrexone use has limited its use in treating alcohol dependence. Nalmefene, another opioid antagonist, has been shown to reduce alcohol craving without any liver toxicity and is now being developed to treat alcohol addiction (Mason, Ritvo, Morgan, et al., 1994; O'Brien, 1997).

Baclofen, a nonopioid muscle relaxant, also exhibits alcohol anticraving effects through modulation of GABA (gamma-aminobutyric acid) and dopamine neurotransmitters (O'Brien, 1997).

Mecamylamine appears to block environmental cued craving of cocaine addiction and is currently in development for this indication, along with its development as a nicotine anticraving medication (Reid, Mickalian, Delucchi, Hall, & Berger, 1999).

Bupropion approved for the treatment of nicotine craving is also in development as a cocaine and methamphetamine anticraving medication. Bupropion research demonstrated that it prevented nicotine craving in patients who did not have symptoms of depression, which indicates that it lessens craving by another unknown mechanism. Similarly SSRI antidepressants like paroxetine decrease alcohol use in even non-depressed alcoholics (O'Brien, 1997).

The craving response is physiologically similar to a body stress reaction. This has led researchers to study drugs that can antagonize corticotropin releasing factor (CRF) that triggers the stress reaction in the brain. The hypothesis is that craving can be prevented by blocking the body's stress reaction. Ketoconazole and CP154,526 inhibit the release of CRF in the brain and are being developed to treat cocaine craving. Metyrapone inhibits the synthesis of body corticoids, which are also involved in the stress reaction. It is also being developed as a drug to treat cocaine craving (Vocci, 1999).

Metabolism Modulation - Medications like disulfiram that can alter the metabolism of an abused drug to render it ineffective or cause noxious reactions when the abused drug is taken are also being developed. The effectiveness of disulfiram relies upon the compliance of the alcoholic to take it in support of their stated desire for abstinence. Historically, antabuse has therefore had limited success in treating alcoholism due to compliance problems. However, the increase of coerced treatment practices like drug courts and probation stipulations during the past decade has improved disulfiram treatment compliance and increased positive outcomes (O'Brien, 1997; Keane et al., 1984; Keane & Fuller, 1986). This has increased interest in the metabolism modulation approach. (Vocci, 1999) One such development is with butyrylcholinesterase (BChE) that increases the metabolism of cocaine to render it ineffective when abused (Dickerson & Janda, 2005).

Restoration of Homeostasis – The homeostasis paradigm for drug addiction was first proposed by CK Himmelsbach in 1941 (Littleton, 1998). Abuse of addictive drugs imbalances brain chemistry that then reinforces the need to continue using the drug. Medications and nutrients that restore brain chemical imbalances are theorized to restore homeostasis and mitigate the need for continued drug use. Drugs that have dopamine-activating effects in the brain (e.g., selegiline, amantadine, pergolide) and antidepressants that increase serotonin in the brain (e.g., desipramine, nefazodone, paroxetine, sertraline, venlafaxine) are all being developed to treat cocaine and alcohol addiction by restoring brain chemical homeostasis (Vocci, 1999).

Amino Acid Precursor Loading - This strategy consists of administering protein supplements (e.g., tyrosine, taurine, d,l phenylalanine, glutamate, tryptophan) to addicts in an effort to increase the brain's production of its neurochemicals and restore homeostasis. Though this strategy has not yet been validated by rigorous research, many treatment programs report good patient treatment compliance and positive outcomes when amino acid precursor loading is added to the treatment process for cocaine, amphetamine, alcohol, and opioid dependence (Blum et al., 1989).

Modulation of Drug Effects & Anti-priming - A fairly recent development is the use of medications that can modulate or blunt the pleasurable reinforcing effects of addictive drugs. Research demonstrates that risk for relapse is great when a recovering addict is primed or uses an addictive substance. Sub reinforcing doses of abused substance or drugs that can block this priming action can decrease relapse. This is the strategy behind the development of low-dose nicotine delivery systems to treat nicotine addiction like the nicotine patch, gum, spray, and inhaler. (Vocci, 1999) Two classes of drugs being looked at for their ability to blunt the reinforcing effects of abused drugs are the calcium and sodium ion channel blockers:

Calcium channel-blocking medications prevent calcium ions from entering brain cells this then blocks the release of dopamine. This prevents the reinforcing effects of cocaine, opioids, and alcohol from occurring. Nimodipine, amlodipine, nephedipine, and isadipine are all calcium channel blockers being developed to treat addiction to cocaine, opioids, and alcohol (Vocci, 1999; Shulman, Jagoda, Laycock, & Kelly, 1998).

Sodium Ion Channel Blockers - Medications like riluzole, phenytoin, and lamotrigine interfere with neuron transmission via blocking the cells uptake of sodium and this enhances the effects of GABA. This results in muting cocaine's reinforcing effects. Cyclazocine, a mixed opioid agonist-antagonist, also reduces cocaine reinforcement by interfering with cocaine's action on presynaptic neurons' sodium ion channels (Vocci, 1999).

Drugs with unknown strategies - Psychedelic drugs like ibogaine and ketamine are said to be effective in treating cocaine and opioid addiction even though the early use of ibogaine to treat opioid addiction had resulted in some fatalities. Dextromethorphan (DM), a nonprescription anticough medication, is being studied to treat opioid addiction. DM has been shown to be a weak glutamate agonist but its mechanism to decrease opiate withdrawal symptoms, craving, and relapse is unclear. Cycloserine, an antibiotic for the treatment of tuberculosis, is being studied for its ability to decrease opioid use by some unknown mechanism. Anticonvulsant medications like valproate and carbamazepine appear to diminish cocaine's craving and "kindling" effects. "Smart drugs", also known as "nootropic agents," are believed to increase brain activity by unknown mechanisms and are also being tested to treat cocaine and stimulant addiction. Camitine/coenzyme Q10, ginkgo biloba, pentoxifylline, Hydergine®, and piracetam are current nootropics being studied for use in cocaine addiction treatment. Tiagabine and gabapentin are anticonvulsant medications used in the treatment of epilepsy. They are believed to increase brain GABA while decreasing glutamate activity but their ability to decrease alcohol, methamphetamine or cocaine relapse occurs by some yet-to-be-discovered mechanism. (Vocci, 1999; O'Brien, 1997) A final, very recent, and really interesting discovery is the potential use of disulfiram to treat cocaine addiction. This oldest FDA approved addiction treatment drug, was found to have aversive effects – increased heart rate, blood pressure, anxiety, paranoia and restlessness - when taken simultaneously with cocaine. Similar to its use for alcohol addiction, disulfiram has been shown to reduce cocaine abuse by causing unpleasant effects if cocaine is used by those being treated with the drug. Although many cocaine abusers also abuse alcohol, this cocaine effect has been shown to be unrelated to its effect on alcohol metabolism. Researches speculate that this

may have something to do with the dopamine enhancing effects of both drugs in the brain but the averse effects seem to occur more in men than in women. (Whitten L: Disulfiram Reduces Cocaine Abuse. NIDA Notes , 20(2): 4-5, Aug. 2005; Carroll KM, et al, Efficacy of disulfiram and Cognitive Behavioral Therapy in Cocaine-Dependent Outpatients: A randomized placebo controlled trial. Archives of General Psychiatry, 61(3): 264-272, 2004; Nich C, et al, Sex Difference in Cocaine-Dependent Individuals' Response to Disulfiram Treatment. Addictive Behaviors, 29(6): 1123-1128, 2004). These and other clinical observations of drugs that lessen addiction or relapse liability indicate that there is a lot more still to be learned about the addicted brain.

Some companies, such as Drug Abuse Sciences, Inc., are developing time-release delivery systems for naltrexone (Naltrel®), methadone (Methaliz®), and buprenorphine (Buprel®). The aim of this development is to improve treatment compliance by having medications injected into the body on a monthly basis.

Patented and Packaged Medical Protocols for Addiction Treatment

These are very recent developments in the treatment of chemical dependency disorders. Entrepreneurs develop medical or clinical protocols to treat addictions and register a patent on their innovation for restricted marketing or copyright treatment manuals for sale to recovery service providers. An example of this is the Prometa® protocol for medical treatment of alcohol and stimulant drug dependence. Prometa employs FDA approved medications (though not approved to treat addiction) in a rigid short-term protocol to abate drug hunger and promote recovery. Medications like flumazemil (Mazicon®, Ro-Mazicon®) are administered in a hospital over 1-2 days along with gabapentin (Neurontin®) and hydroxyzine (Vistaril®) which are continued over the next 30 days. Another example is the Healing Visions Clinic located on the Caribbean Island of St. Kitt uses ibogaine and other medications over 3-7 days for treatment of opioid and other addictions. Ibobaine is banned in the US.

An example of a packaged clinical protocol to treat addiction is the Matrix Protocol for cocaine, methamphetamine and other stimulant drug addictions. Individual treatment manuals, educational resources and video presentations organized around a 90-120 day clinical process that encourages recovery are included in the copyrighted packet for use by addiction treatment providers. Many other manuals or packaged protocols are marketed and they provide valuable tools for addicts to help them address recovery issues like relapse prevention, **Post Acute Withdrawal Symptoms (PAWS),** cognitive impairment, environmental cues, cravings, family and other issues that can trigger slips and addiction relapse. PAWS (sleep, memory, thinking, anxiety, emotional and reflex coordination problems) can last for several months to years of abstinence (Gorsky, T & Miller, M, Staying Sober: A Guide for Relapse Prevention. Herald House Independence Press: Independence, Mo., 1986).

An increased documentation of **cognitive deficits** during early recovery (impairments of learning, attention, perception, information processing, memory, temporal or time processing, cognitive inflexibility, problem solving, abstract thinking and even physical coordination) also last for several months after initiation of abstinence from drug or alcohol abuse (Taleff MJ, Alcohol-caused Impairment and Early Treatment. Counselor, Magazine for Addiction Professionals, 5(1): 76-77, 2004).

VIII. Conclusion and Questions

Treatment Works! Outcome studies like CALDATA, CalTOP and DATOS document positive treatment outcomes for drug and alcohol addiction including methamphetamine:

- Continued 3 to 5 year abstinence for almost 50% of those treated (CALDATA)
- Research on Matrix Model and CalTOP analysis by Dr. Y-I Hser of 43 treatment programs and 1,073 primary methamphetamine abusers validate 87% continual abstinence rate for period of at least 9 mo. To 1 year (Hser, Y.-I.; Evans, E.; and Huang, Y.-C. Treatment outcomes among women and men methamphetamine abusers in California. *Journal of Substance Abuse Treatment* 28(1):77-85, 2005.)
- 74% decrease of crime in those treated (CALDATA)
- Actual $7 - $12 savings for ever $1 spent on treatment; ONDCP research found $7.46 saved for every dollar spent across the US. A meta-analysis of more than 1000 addiction treatment outcome studies conducted by the University of Pennsylvania and released in March 2005 documented cost savings ranging from 33 cents to $39 for every $1 spent in all studies analyzed. None of the studies could document any loss from money invested in drug abuse treatment. (Belenko, S., Patapis, N. and French M.T., Economic Benefits of Drug Treatment: A Critical Review of the Evidence for Policy Makers. Missouri Foundation for Health, February 2005 at http://www.tresearch.org/resources/specials/2005Feb_EconomicBenefits.pdf accessed 11/16/06)
- Minimum 6 to 8 months continuous treatment needed for positive results (CALDATA)
- Alcohol treatment had best results and heroin the worse with methamphetamine treatment in between those two outcomes (CALDATA)
- Group therapy showed better outcomes than just individual counseling (CALDATA)
- "Coerced" treatment (Drug Courts, probation, parole) have as good if not better outcomes than voluntary treatment (Brecht ML, Anglin MD and Jung-Chi W, Treatment effectiveness for legally coerced versus voluntary methadone maintenance clients. Am J of Drug and Alcohol Abuse, March 1993)
- Cultural consistent treatment had better outcomes than generic treatment models (CALDATA)
- Also well documented positive outcomes of substance abuse treatment are reductions in psychiatric problem (greater than 40%), family and social problems (50-60%), other medical problems (15-20%) and employment problems (15-20%). (The California Treatment Outcome Project [CalTOP] Final Report, Executive Summary: i-vi, UCLA Integrated Substance Abuse Programs, Updated, Nov.20, 2003)

Recommended Reference: Inaba, DS & Cohen, WE: *Uppers, Downers, All Arounders – Physical and Mental Effects of Psychoactive Drug, 5th Edition.* CNS Publications, Inc.: Ashland Or. 2003

EVALUATION

1. Which of the following is **not** a current ONDCP strategy to reduce the abuse of drugs in the US?
   a. Treatment payment vouchers for recovery counseling especially at faith based treatment centers
   b. Increase drug testing at schools to identify and punish drug experimentation by youth
   c. Provide more funding resources for Demand Reduction than for Supply Reduction efforts since treatment and prevention are more effective
   d. "Fusion Technology" = Combine efforts of DEA, Dept. of Defense, Dept. of Homeland Security and all US Attorney General Offices
   e. Counterdrug Technology Assessment Center to develop new resources to combat drug trafficking

2. Which of the following is **not** a current issue to chemical dependency treatment developments?
   a. Availability of sufficient resource to provide "treatment on demand to those who want or need it
   b. Development of more effective technology to diagnose addiction and better match addicts to the specific treatment interventions
   c. Expanding development and use of drugs to treat drug addictions
   d. Increased emphasis on employment of only evidence-based best treatment practices
   e. Growth of criminal justice system initiated treatment participation

3. What medication is **not** FDA approved for treatment of chemical dependency?
   a. Naltrexone for treatment of opioid dependence
   b. Naltrexone for alcohol dependence
   c. Bupropion for nicotine dependence
   d. Varenicline for nicotine dependence
   e. Imipramine and anti-depressants for cocaine or methamphetamine dependence

4. Which of the following are **not** medication strategies in development to treat chemical dependency?
   a. Antagonist, mixed agonist-antagonist, and vaccines
   b. Replacement drugs or agonist
   c. Rapid opioid detoxification and medication treatment protocols
   d. Anti-craving medication and agonist anti-priming
   e. Diuresis and laxatives to increase body clearance of drugs

5. The Modulation of Drug Effect addiction treatment strategy is best described by which of the following?
   a. Medications that lessen symptoms of withdrawal and craving or facilitate detoxification
   b. Drugs that restore the brain's natural chemical balance or homeostasis

c. Protein, vitamins and other nutritional supplements to promote more rapid restoration of the brain's natural chemical balance or amino acid precursor loading
d. Substances that blunt the pleasurable or reinforcing effects of addictive drugs or sodium and calcium ion channel blockers as well as low doses of nicotine
e. Prescribed medications that act like and substitute for the illicit drug addiction or agonist replacement therapies

6. T F The average potency of street marijuana today is much greater than that of the 1960's

7. T F Since about the 1980's many new sources of street heroin has resulted in a dramatic increase in the average potency of this illicit substance

8. T F Smoking free base cocaine results in less euphoria or rush than snorting powder cocaine

9. T F Methamphetamine in the racemic d,l form is 3 to 4 times more potent than just d-isomer methamphetamine

10. T F Chemical Dependency Treatment Outcome studies demonstrate that viable long-term abstinence, crime reduction, cost saving and even positive family outcomes of decreased medical/psychiatric, employment, family and social problems are realized by treatment of addicted individuals

[Answers: 1. c; 2. a; 3.e; 4. e; 5. d; 6. T; 7. T; 8. F; 9. F; 10. T]