METHADONE MAINTENANCE THERAPY: A Theory and Practice Primer

Prepared by
Brian Coon, MA, CADC, MISA II
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Preface

Disclaimer:
The intended audience of the present paper is the student or professional in the behavioral health industry. The author has made a partial review of the literature on the subject of Methadone Maintenance Therapy (MMT) and compiled a synthesis of information, empirical research findings, philosophies, practice guidelines and regulations in the field of MMT. The paper is not intended to serve as an adequate training that can stand alone as an authoritative statement on MMT. Some opinions expressed are rhetorical expressions of the author. Inclusion of references and suggested links do not necessarily imply agreement of the author with statements found in those resources.

About the Author:
The author holds a Bachelor of Science degree in Psychology and a Master of Arts degree in Community Clinical Psychology, both from Bradley University, and is certified by the Illinois Alcohol and Other Drug Abuse Professional Certification Association as an Alcohol and Other Drug Abuse Counselor (CADC). He has worked full-time in the substance abuse treatment field as a counselor for over 17 years, providing clinical supervision and training to undergraduate and graduate students and clinical counselors in the field for over 14 years. He serves as the clinical and administrative supervisor of the outpatient Methadone Maintenance program, in his role as Manager of Human Service Center Substance Abuse Services in Peoria, Illinois

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Introduction

Opioid dependence disorders are chronic, progressive, often fatal and characterized by relapse in spite of treatment. Increasing availability of increasing quality of heroin at decreasing prices are recent contributing factors to the opioid dependence problem. Related illnesses such as hepatitis B, HIV/AIDS and STD's compound the problem. The cost of opioid dependence disorders and related problems to members of the private and public sector is very large. Crime rates, criminal justice system over-crowding, health care costs, un- and under-employment rates, homelessness, and prevalence rates of child abuse and neglect are all adversely affected by the opioid dependence problem.

The paper begins with an overview of Methadone Maintenance Therapy Defined. This first section of the paper covers areas such as: what is MMT and who is appropriate for admission, the pharmacokinetics of methadone, staff qualifications, the team approach to patient care, and the goals of symptom management, harm reduction and maintenance strategies. Theories are applied to MMT next, as part of the conceptual underpinnings related to the psychology of MMT and its patients. Specifically, these theories are principles related to psychophysics and the conditioning theories of addictions. Treatment factors are also reviewed, including: depth of processing during psychotherapy, reinforcement for treatment compliance and punishment for non-compliance. Controversies from within and without the MMT field are explored. This section of the paper discusses the argument that MMT is merely "substituting one drug for another." The question of long-term methadone maintenance vs. a drug-free goal is discussed, as is the question of dispensing a relatively high dose vs. a low dosing practice. Changes in dispensing and regulation are also briefly mentioned. Finally, MMT Efficacy is reviewed, including: efficacy studies, Methadone vs. LAAM vs. Buprenorphine vs. Naltrexone, and the impact of stereotypes of methadone maintenance patients.

Methadone Maintenance Therapy Defined

What is “Methadone Maintenance Therapy?”
Who is appropriate for MMT?
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What is “Methadone Maintenance Therapy”?

Methadone maintenance therapy is a *blend* of biopsychosocial interventions. The pharmacological intervention of dispensing daily doses of orally ingested methadone within the context of addiction-specific primary and psychiatric healthcare constitutes the biological component. The intervention of addiction- (and other psychiatric disorder if pertinent) specific psychotherapy and support constitutes the psychological component. The intervention of community-based supportive casework services within the recovering context of peers in methadone maintenance treatment constitutes the social component.

An overview of the practice of MMT and the medical/political context in which it is currently delivered is found in the American Medical Association’s statement of the National Consensus Development Panel (1998) on Effective Medical Treatment of Opiate Addiction. One review of the history and development of methadone and the treatment modality of methadone maintenance therapy is Murray (1998). Ball and Corty (1988) present a brief overview of basic issues related to MMT. A more comprehensive and detailed review of the theory and practice of MMT is found in the State Methadone Treatment Guidelines (Center for Substance Abuse Treatment, 1993). The pharmacological and psychosocial treatment components of MMT are summarized and detailed below.

The pharmacological properties of **methadone** are long established. Methadone, a synthetic **opiate**, binds to the **receptor sites** that naturally exist in the human body for receipt of the body's own **endogenous morphine (endorphin)** and related compounds. These are the same receptor sites that accept the metabolic products of other opiates, including heroin. As the pharmacological action of methadone in the opiate receptor site is similar to that of morphine (a metabolic product of heroin), methadone meets the definition of an opiate **agonist**. However, the action of and **withdrawal** from methadone differ from that of morphine. When administered orally, methadone produces a delay in onset, a lowering of peak effect and an increased circulating **half-life**; likewise, its withdrawal syndrome is slower in onset with a prolonged course and less severe symptoms. Although heroin's half-life typically requires administration every four to six hours for maintained effect, methadone maintains its therapeutic effect twenty-four hours or more.

Methadone maintenance therapy is predicated on adequate dosing. ***A priori*** assumptions biased against adequate dosages can result in over-medication (intoxication above the level of **tolerance**) or under-medication (withdrawal syndrome below the level of dependence). Dosing within an adequate range (a blocking dose) achieves a physiological **homeostasis**. Subsequent administration of additional opiate produces no **euphoria** due to the high tolerance to the (pure) methadone, while daily dosing produces relatively stable blood levels and results in

no withdrawal syndrome. Therefor, incentives for opiate acquisition and consumption are reduced significantly if not completely. The blocking methadone dose is set above the level of dependence (to prevent withdrawal) and below the level of tolerance (to prevent euphoria). One approach for dose determination is to slowly increase the daily dose beyond the initial dose required for stabilization to a higher level of tolerance. Theoretically, the higher dose will saturate available receptor sites and prevent any possibility of euphoria or continued reward for further opiate use. Establishment of a blocking dose range is aided by drug toxicology screening, client report of withdrawal or intoxication **symptoms**, and staff observation of withdrawal or intoxication **signs**. Toxicology screens positive for opiate other than methadone would apparently indicate an insufficiently high dose of methadone, especially when attempting to achieve stabilization.

Methadone maintenance therapy from a cooperative team approach utilizing qualified physician, nursing and counseling staff assists patients in stabilizing their addiction signs and symptoms, reducing the related drug acquisition lifestyle, and establishment of positive lifestyle action with appropriate community support. It may be considered analogous to long-term psychiatric management of a chronic mental disorder through medication and counseling, thereby achieving symptom reduction and enhanced self-care, or management of insulin-dependent diabetes where harm reduction and stabilization are the goal. When combined with psychosocial therapeutic ingredients such as relapse prevention planning, stress management training, family-focused therapy, communication skills development, vocational counseling and case management assistance with accessing community resources for overall recovery program support of their lifestyle, the client may be expected to achieve long-term **abstinence** from illicit drug consumption and full participation in any possible range of normal lifestyle functions. When achieved, individualized decisions may be made about the merits of continued maintenance verses slow withdrawal from methadone by the client/staff team responsible for the case.

The pioneering work related to the theory, practice and initial empirical study of MMT is foundational reading (Dole & Nyswander, 1965; Dole & Nyswander, 1967; Dole, Nyswander & Kreek, 1966). Dole (1980) reviews the state of the MMT modality from its inception to the date of his writing in 1980, as do Zweben and Payte (1990) at the time of their writing. Dole (1994) answers the question, “What have we learned from three decades of methadone maintenance treatment?”

Who is Appropriate for MMT?

Who should receive MMT? What are the indications for starting MMT? Who is appropriate for admission into a MMT program?

In short, MMT is designed for the chronic opiate dependent person who can not reasonably expect to recover through drug-free based self-help and/or professional treatment efforts. MMT may also be appropriate for those who may not be available for residential treatment due to various biopsychosocial circumstances.

The regulations of the Food and Drug Administration (FDA) from 1995 require that MMT patients live within a 50 mile radius of their home clinic. Preventing the diversion of methadone to individuals other than the patient, and preventing double-dosing by a patient concurrently enrolled in more than one MMT program, are among the reasons for such a policy. Specific

provisions exist in admission criteria for those seeking services from a penal or chronic care setting, namely, that the patient need not show **physiological dependence** to qualify for admission. This policy is meant to prevent a return to use of illicit opiates, relapse of the opioid dependence disorder, and reduce harm for the patient (while also protecting the community from drug-related crime).

Many states have adopted the Patient Placement Criteria (currently in its second edition, the PPC-2) of the American Society of Addiction Medicine (ASAM) as the clinical guideline set for determining appropriateness for admission, continued service and discharge of MMT patients (American Society of Addiction Medicine, 1996). Among ASAM criteria are an opiate dependence diagnosis according to the criteria found in the American Psychiatric Association's (1994) Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) plus meeting specific criteria on ASAM's six dimensions of assessment (acute intoxication/withdrawal potential, biomedical conditions and complications, emotional/behavioral conditions and complications, treatment acceptance/resistance, relapse potential and recovery environment).

Methadone: Pharmacokinetics

This section will first review some basic information related to opiate receptors. Secondly, methadone per se will be explored, including its action, effects and drug interactions.

Opiate receptors fall into five major subtypes: mu (μ), kappa (κ), sigma (σ), delta (δ) and epsilon (ε). Discussions (beyond the purpose of the present paper) of cellular processes related to opioid receptor structure and function are found in reviews by Gold and Miller (1992), Mestek, Chen and Yu (1996), Nestler (1996), Nestler and Aghajanian (1997) and Raynor, Kong, Law, Heerding, allent, Livingston, Hines and Reisine (1996). A few points are summarized here, however. Commonly available **narcotic analgesics** can be defined by their activity at three receptor sites: delta, kappa and mu. The δ receptors seem to have a high binding affinity for **enkephalin** and beta-endorphin and a low affinity for **dynorphin** (both are endogenous **ligands** for opiate receptors). The μ receptors mediate morphine-like supraspinal analgesia, euphoria and respiratory and physical depression. The κ receptors mediate **pentazocine (Talwin)**-like spinal analgesia, sedation and pupil dilation. The κ receptors have a high binding affinity for dynorphin A and a low affinity for enkephalin. The μ receptors have a high binding affinity for enkephalin and beta-endorphin. The σ receptors mediate **dysphoria**, **psychotomimetic** effects and respiratory and **vasomotor** stimulation caused by drugs with antagonist activity.

The **pharmacokinetic** properties of methadone are of importance in the efficacy of MMT. These properties of methadone are long established. The peak blood **serum** level after administration occurs approximately between 2 and 4 hours after ingesting oral methadone; the circulating half-life of methadone is around 24 hours (Inturrisi & Verebely, 1972). These are both much longer than the peak and half-life of heroin. The duration of therapeutic effect for the stabilized MMT patient is between 24 and 36 hours on the average, although being a "fast metabolizer" or being on certain medications may increase or decrease the **bioavailability** of methadone. In the average stabilized MMT patient, the peak serum level is less than twice the trough serum level. The generally accepted minimum serum level for maintenance of patients is regarded by various practitioners as 150 **ng/ml**, or as much as 400ng/ml or more (see Loimer and Schmid, 1992 for a brief review). This question is the focus of much current empirical investigation. Research has demonstrated a lack of differences across psychophysiological

indices for various serum levels during maintenance treatment with methadone (Loimer, Schmid, Grünberger, Jagsch, Linzmayer & Presslich, 1991). This means that the stabilized MMT patient may complete a wide range of life skill and work tasks without significant impairment, or at least otherwise be indistinguishable from the general population not on MMT.

Overall, methadone produces a delay in onset of effect, a lowering of peak effect and an increased circulating half-life with a slower onset for withdrawal and less severe withdrawal symptoms than heroin or morphine. Although these principles are generally true, it is important to note that individual differences, based partly on pharmacogenetics, exist in the metabolism of, and interaction between, various drugs including methadone (Grudzinskas, Woosley, Payte, Collins, Moody, Tyndale & Sellers, 1996). These differences may, for example, affect the rate of change in serum level of methadone over time after ingesting a dose of methadone. One study (Holmstrand, Änggård and Gunne, 1978) found that average distribution of methadone in their patients increased to a plateau in 8 to 10 days of maintenance treatment and then fell; significant individual differences were found as well. Such factors are important to take into consideration in individual patient management. For example, a patient may require an increase or decrease in dose due to their individual biochemistry.

Rifampin, **phenytoin (Dilantin)**, **carbamazepine (Tegretol)** and opioid agonists or antagonists may all play a role in precipitating withdrawal syndrome, as they are medications known to accelerate methadone metabolism; **Ethyl alcohol** is known to potentiate methadone, then effect onset of withdrawal syndrome (Center for Substance Abuse Treatment, 1993; Gitlin, 1996). Some patients are known to differ significantly in the rate of methadone metabolism; **ketoconazole** slows methadone metabolism and has been used adjunctively to maintain adequate methadone serum levels in patients that are “fast metabolizers” of methadone (DePetrillo, Camara, Owen & Flockhart, 1999).

Methadone is known to produce analgesia, constipation and suppress respiration (dose and time-dependent effects). Over-dosing may cause death. Sensitivity to methadone is found in some patients, as is a paradoxical reaction that may include loss of sleep, over-alert and anxious mental status with restless behavior. Methadone is not known to cause any tissue or organ damage, and is relatively safe during pregnancy (especially in comparison to the use and impact of street drugs and the addiction lifestyle on the fetus). Reviews of this work may be found in the State Methadone Treatment Guidelines: Treatment Improvement Protocol (TIP) Series # 1 (Center for Substance Abuse Treatment 1993), Chudoba (1997), Jarvis & Schnoll, (1995) and Miller (1994). One possible benefit of methadone besides its indicated therapeutic value in MMT may be the slowing of human immunodeficiency virus (HIV) expression in the brain (Chao, Gekker, Shuxian, Sheng, Shark, Bu, Archer, Bidlack, & Preston, 1996). Morphine appears to have additional, possibly negative, impacts related to human immune systems (Yeager, Colacchio, Cecelia, Hildebrandt, Howell, Weiss & Guyre, 1995).

Staff Qualifications

Practice guidelines stress the necessity of specifically trained experienced professional who can appropriately relate with the population (Center for Substance Abuse Treatment,1993; Food and Drug Administration, 1995). Various funding agencies and state regulatory bodies address credentialing specifics that must be met if they apply. Recognition of subjective and objective evidence for starting or changing opiate dose in an opiate addict who is self-reporting facts,

feelings and opinions requires special knowledge and skill. The doctor, nurse and counselor must approach the patient with an empathic, non-judgmental view based on appropriate training and experience to properly assess, plan and render services. The members of the staff team must have adequate preparation and supervision to deliver the expert services required for the population in general, as well as specific needs of the case, and to refer the patient as needed.

Team Approach to Patient Care

The patient, counselor, nurse and physician constitute the core of the treatment team in MMT. Certainly no one reports their own symptoms, undergoes treatment or takes the patient's methadone other than the patient. Certainly no one takes the physician's interview and physical exam, prescribes the methadone or approves changes in the prescription other than the patient's physician. Certainly no one sets up and dispenses the methadone, or completes the vast majority of the medical documentation other than the patient's nurse. Certainly no one integrates data and delivers counseling and related services other than the patient's counselor. Each member of the team therefor has a unique and necessary contribution to initial and ongoing assessment and treatment planning.

Empirical investigation demonstrates the efficacy of what is recommended by the majority of practitioners and even Federal (Food and Drug Administration, 1995) regulators: a team approach (Kang, Magura, Nwakeze, & Demsky, 1997). Decision making about dosing, clinical privileges such as take-home bottles, and other treatment planning concerns should not be done without the input of the patient. In fact, seeing the patient as a member of the treatment team, and actively involving the patient in the decision making process tends to contribute to positive outcomes. Those patients who are isolated from participating in the decision making process about their treatment tend to have poorer outcomes. D'Aunno and Vaughn's (1992) national study of MMT clinics found 34% of units reported their patients were aware of their dose to some, little or no extent.

Symptom Management, Harm Reduction and Maintenance Strategies

Needle cleaning kits, needle exchange programs, informational brochures and classes, free condom distribution, government-sponsored/controlled heroin distribution centers, legalized street drugs, legalized use of street drugs and similar practices can be thought of as harm-reduction strategies. Harm reduction strategies seek to limit the negative impact, or harm, caused by (for example) addiction, by limiting the danger involved in the practice of addiction and its related lifestyle. The philosophy and practices of harm reduction are controversial separately and together.

Various critics and advocates of MMT consider MMT to be a harm reduction effort; some individuals either criticize it or advocate for it on that basis alone. MMT, in its essence, is a symptom management strategy. It seeks to stabilize the symptoms of addiction and the addiction lifestyle. The role of treatment for diabetes (insulin plus the supportive psychosocial services within the context of which insulin is prescribed and taken) may be used as an imperfect analogy for MMT. So may the blend of biopsychosocial services for the seriously and persistently mentally ill. As such, MMT does not "cure" the root "cause" of opiate addiction. MMT then, would not be thought of from the outset of treatment as having a terminal end.

Rather, MMT is generally conceptualized as a long-term maintenance strategy where stabilization is the goal.

Regardless of one's position on various proposals of specific and controversial harm reduction efforts (such as needle exchange programs), Wenger and Rosenbaum (1994) discuss the advantages and disadvantages of a treatment-on-demand approach to providing availability of MMT treatment to those who need it. They report on an ethnographic study of IV drug users and their difficulties while waiting for admission, or enrollment, into a treatment slot for MMT. Areas of concern that are significantly improved by MMT include HIV transmission rates, extent of needle sharing, and extent of disease progression among others. Barriers to treatment created by finite and usually inadequate numbers of treatment slots, patient costs for treatment, the difficulties of the waiting list process, and a lack of coping mechanisms while waiting for a treatment slot are reviewed. The effects and implications for the individual patient and MMT treatment candidates as a population are discussed, as well as the impact on society at large. Their study includes examples of patient responses from structured interviews that were of a quantitative and qualitative nature.

Treatment access on demand for MMT seems like a less controversial and more advantageous harm reduction effort. Wenger and Rosenbaum discuss methods of program implementation. One option is a treatment entry program with a low threshold/criteria for treatment readiness. This would allow easier access to treatment on demand with greater attractiveness to patients, including a bypass of extensive screening measures. Coupled with a non-punitive approach, patients who become stabilized could progress to higher threshold maintenance programs. The beneficial impact on the addicted population, MMT treatment system and society at large of no- or low-cost MMT on demand is potentially great and appears less controversial and more clinically acceptable than more controversial harm reduction approaches.

Rosenbaum, Washburn, Knight, Kelley and Irwin (1996) elaborate on the impact of (de)funding MMT in its context as a harm reduction effort. Their paper describes the negative impact of reducing or eliminating publicly funded MMT in terms of: drug use, crime, unemployment, HIV risk and gender role victimization. Their policy recommendations include: treatment on request, ending limited-duration treatment when imposed only by policy, and the need to view MMT clients as patients and consumers of healthcare.

Dole (1994) discusses broad availability of MMT programs, the advantages and limitations of the MMT modality, the price of preoccupation with short-term and abstinence goals, and the therapeutic social and political context within which administration of MMT is most beneficial. He also discusses disadvantageous social and political contexts within which MMT was initially implemented, and the resulting loss of effectiveness: insufficient dosing, premature discharges, inadequate numbers of treatment slots, time wasted in controversy, lack of stabilizing physical health problems, and continued judgment of the addicted.

Theories Applied to MMT

Psychophysics: The JND and "the pain-sensitive opiate addict"
Conditioning Theories of Addictions

Psychophysics: The JND and "The Pain-Sensitive Opiate Addict"

The background of **psychophysics** (Lundin, 1985) and its applicability to MMT is now explored**.** Ernst Weber (1795-1878) examined the ability of subjects to discriminate differences in the weights of objects by lifting them, with the limit or threshold being the "just noticeable difference" (JND). Weber noticed the ability of subjects to discriminate was dependent upon the ratio of one weight to the other, and that the size of the JND was therefore not an absolute amount. This principle, which became known as Weber's Law, was stated in a formula by Fechner (1801-1887). Fechner noticed an arithmetical increase in sensation magnitude of JND's required a geometric increase in physical magnitude to produce the effect (establishing a logarithmic relationship between the two: Fechner's Law).

JND's were determined experimentally by three methods. Weber and Fechner used a method called the *method of constant stimuli* in which variable stimuli were compared with a standard stimulus, and the JND thus determined. Fechner used the *method of average error*, in which a person could adjust one stimulus to meet the standard of a constant stimulus; the JND was the amount of average error after many attempts. Fechner's *method of limits* employed two identical stimuli, one of which was changed until a difference was detected; the average threshold, then, was the amount of the JND.

The intensity of initial stimulus, then, determines the size of the JND. The smaller the intensity of initial stimulus the smaller the JND. The larger the intensity of the initial stimulus, the larger the JND. For example, if a blindfolded subject holds a 16 pound bowling ball in each hand with arms outstretched, how many paper clips (how much weight) must be added to <u>one</u> of the hands before a just noticeable difference is detected? Alternatively, if a blindfolded subject holds 10 paper clips in each hand with arms outstretched, how many paper clips (how much weight) must be added to <u>one</u> of the hands before a just noticeable difference in weight is detected?

How can these concepts be applied to MMT? Opiate action includes the effect of analgesia. Analgesia is conditionable and subject to tolerance (Siegel, 1976). Less so, however, in those individuals with a heroin addiction as compared to the methadone maintenance patient. Why? The duration of action of heroin is only a few hours, compared to methadone, which is 24 hours or more. Other differences in the pharmacological action of heroin over methadone exist as well, such as the time required to reach peak effect (much more rapid with heroin, when compared to methadone). Additionally, those individuals with a heroin addiction do not achieve and maintain steady-state physiological maintenance status as a result of their heroin use. Rather, they bounce from changing intensities and durations of euphoria to withdrawal, and back again. Methadone maintenance patients, conversely, do not experience euphoria or withdrawal, and are maintained on steady levels of circulating pharmacological opiate. The regularity of the MMT patient visiting the clinic for daily dosing (normalized, non-pathogenic drug acquisition behavior), avoiding illicit drug-associated environments, and not illicitly administering opiate also serve to modify the interaction of the intero- and extero-ceptive cue context of opiate

(methadone vs heroin) administration. These variations limit the extent to which the analgesia is subject to tolerance for heroin use, compared to methadone use.

One result in those with a heroin addiction is the phenomenon of pain sensitivity. Frequently experiencing analgesia means such an individual lives much of the time with a perceived low intensity of initial stimulus. As such, JND's for pain or touch would predictably be small relative to a control group not addicted to heroin. The self-report of many individuals with a heroin addiction is that what is barely noticeable to many people is to them painful or at least quite irritating (e.g. their clothes feel scratchy). The clothing feels more irritating when compared to the lack of feeling that they normally experience.

Additionally, the avoidance-based lifestyle of the chronically and physiologically dependent person with an opiate addiction produces **hypervigilance** and over-attending to possible subtle indications of the onset of withdrawal syndrome. As a result, patients' subjective reports of withdrawal symptoms do not necessarily correlate with objective withdrawal signs (Hiltunen, Lafolie, Martel, Ottosson, Boreus, Beck, Borg & Hjemdahl, 1995). In fact, a methadone detoxification phobia has been theorized, found empirically and described in the literature (Latowsky, 1996). One study (Holmstrand, Änggård and Gunne, 1978) noted the difficulty in establishing the connection (difference) between patient neuroticism and complaints about methadone dose. Loimer and Schmid (1992) studied self-report and observer ratings of withdrawal across plasma levels and found the best outcomes at 90 mg of methadone or more. Withdrawal symptoms were reported, however, in patients with plasma methadone levels greater than 600 ng/ml. Loimer and Schmid concluded that rating scales of withdrawal, plasma levels of methadone and urine testing should all be used together to maximize treatment outcome, especially given the typical fear of withdrawal in opioid addicts.

Regardless, withdrawal from **psychological dependence**, any (even mild) physiological and/or psychological discomfort, and also interpreting various physical and/or psychological phenomena as opiate withdrawal syndrome, add to the discomfort subjectively experienced by the person with a heroin addiciton. Further complicating the problem is the fact that such real or imagined psychological and/or physiological states may also serve as cues that themselves elicit conditioned withdrawal syndrome. This conditioned withdrawal syndrome can include physiological changes as real and aversive as actual opiate withdrawal itself. Taken together, the perceived discomfort level of the above mentioned aversive states is even higher than might be expected, given the relatively small JND's in the perceptual experience of the individual with a heroin addiction.

The basic approaches of psychophysics discussed above are now reviewed in the context of MMT. The *method of constant stimuli* is applied to MMT. What variable stimulus is compared with a constant stimulus? Testing (tasting) the variable quality of several bags of heroin against the constant of the best bag the individual has ever sampled. The *method of average error* is applied to MMT. How does the person with a heroin addiciton adjust one stimulus to meet the standard of a constant stimulus? Setting up correctly prepared doses of heroin to meet the demand of the constant stimulus of the withdrawal syndrome. The *method of limits* is applied. What two identical stimuli are compared, with one changed until a difference is detected? To prevent overdose and/or to avoid selling or giving away too good a shot, the person with a heroin addiction is motivated to detect the slightest increase or decrease in quality of a bag or shot.

In short, the individual with a heroin addiction lives in a perceptual experience (relative to the general population) characterized by extreme reference points for pleasure and pain, reduced limits of frustration tolerance and a motivation characterized by pursuit of euphoria, or at least escape from and/or avoidance of pain. The rewards of addictive behaviors generalize to reinforce addictive thinking, and the punishing consequences of not participating in the addiction are large. It is to conditioning theories of addictions that we now turn.

Conditioning Theories of Addictions

Pavlov's conditioning paradigm consisted of an initially neutral cue reliably preceding a stimulus that unconditionally produces a response; after repeated pairings the once neutral cue (now a **conditional stimulus**) comes to produce a **conditional response** very similar to the **unconditional response**. The classic preparation of this paradigm included a bell as the conditional stimulus (CS), meat as the unconditional stimulus (UCS), salivation in response to the meat as the **unconditional response** (UCR), and salivation in response to the bell alone as the conditional response (CR). Salivation in response to the meat happens unconditionally, but salivation in response to the bell is conditional upon repeated pairings: ringing of the bell just before presentation of the meat.

Pavlov himself suggested that drug administration fit this conditioning paradigm. For example, the pharmacological action of heroin would be the UCS, the UCR's would include euphoria, and a warm sensation, and the CS's would be the drug-administration environmental cues (such as money, spoons and syringes). Siegel (1979) has noted the CR in the drug administration paradigm, however, is in the *opposite direction* of the UCR; it serves as an attempt of the body to counter the drug effects and preserve physiological homeostasis. For example, the UCR in the heroin use scenario would include euphoria, a warm feeling, relaxed muscles, slowed rate of heartbeat and respiration, and a "nod." Exposure to drug-predictive conditional stimuli produces conditional responses that are *anticipatory* and in the *opposite direction* of the drug effects. In other words, the conditional responses are *drug-compensatory*. Thus, anxiety, irritability, chills, sweats, increased heart and respiration rate would result from mere exposure to the conditional stimuli, regardless of whether or not the drug was actually administered (O'Brien, Testa, O'Brien, Brady, & Wells, 1977).

Furthermore, and problematically, these drug-compensatory conditional responses (which may be considered conditional withdrawal) can be elicited by presentation of the right cue(s) under the right conditions of **saliency**, even when the addict is sober or has years of sobriety. Conditional responses that have not been **extinguished** are subject to significant display under the right cue context: the relationship between drug acquisition/use cues and the administration of drugs still exists in a strong enough way to promote homeostasis preserving attempts by the body to mitigate unconditional drug effects (Koob & LeMoal, 1997; Kreek & Koob, 1998). Siegel and Larson (1996) report on the disruption of conditioned tolerance by (mere) presentation of an extraneous external stimulus; they note that some instances of drug toxicity or overdose (unexpectedly large drug effects) are in part due to this process and that conditional responses to conditional stimuli within extraneous contexts (such as arrival of the police) should be assessed.

Taken together, then, tolerance, craving, physiological withdrawal, psychological withdrawal, thresholds to experience euphoria, and overdose are conditionable phenomena (MacRae, & Siegel, 1997; O'Brien, Testa, O'Brien, Brady, & Wells, 1977; Wikler, 1965, 1967 & 1973) that

are produced and mitigated, at least in part, by the cue context in which drug administration occurs. The inter-relationships between and among cues affect these phenomena as well (Rescorla, 1988, 1992). As such, a UCS may produce different UCR's or a CS may produce different CR's depending upon the hierarchical context in which the conditioning and response elicitation are produced. One must employ careful consideration in developing an accurate cue-response synopsis for any particular patient, and attempt to eliminate bias in the process; this has proven difficult even for researchers working with morphine dependent rats (McDonald & Siegel, 1998). Drug-related interoceptive (internal) cues may include thoughts of using, emotions and sensory/perceptual content and processes. Additionally, the authors of one report investigating the relationship between plasma methadone levels and indications of withdrawal, noted that patient expectancies of the effects of methadone probably existed as a confounding factor (Hiltunen, Lafolie, Martel, Ottosson, Boreus, Beck, Borg & Hjemdahl, 1995). McDonald, Parker and Siegel (1997) report on the morphine-use state itself as a discriminative stimulus (or interoceptive cue) in the learning processes associated with drug use, and discuss the relevance of state-dependent learning as a factor to consider in clinical addictions treatment. Drug-related exteroceptive (external) cues are found in the environmental context of drug acquisition and drug use behaviors. Examples of cues contributing to the type and extent of conditional responses include: temptation to use, saliency of use cues such as money, syringes or neighborhoods, and whether or not the drug is self-administered or passively received (such as an automated IV drip).

A further consideration is from an operant (rather than Pavlovian) conditioning perspective. These CR's are also aversives that generally serve as punishers. Return to the use of opiates, a relapse, alleviates the apparent withdrawal syndrome, thus serving as a special type of reinforcer: a negative reinforcer (increasing the frequency of opiate use by the removal of an aversive stimulus). Spiga, Grabowski, Silverman and Meisch (1996) completed a study of self-administration of methadone in MMT patients. A button pressing response was required of the subjects to cause the dispensing machine to release a dose of methadone. Response ratios of either 32, 64 or 128 presses per administration were required, and methadone was dispensed at either 0.027, 0.054 or 0.108 mg / ml in 10 ml of oral solution. The researchers found that: even small amounts of methadone were reinforcing, self administration was reduced as the number of required presses increased, but that at the highest concentration of methadone (0.108 mg / ml) the total amount of methadone ingested was relatively unaffected by the number of required responses. "Unit price" of methadone was defined by the researchers as the response requirement divided by the reinforcer magnitude. This may be clinically relevant as one may determine the patient's level of investment in the opioid acquisition lifestyle, and quality and quantity of investment (or motivation) in treatment participation, compliance and living in a daily recovery program and lifestyle.

Extinction (of both operant response rates and occurrence of Pavlovian CR's) turns out to be more complex than simple cue presentation and/or withholding of reinforcement while responses decline. Associative relationships between and among cues, responses and outcomes (such as reinforcements and withholding reinforcers) have been described (Rescorla, 1997). Patient education related to conditioning theories of addictions, symptom prescriptions of future psychological and physiological reactions to internal and external stimuli, and skill training in coping with the extinction process would seem warranted, if only to build self-efficacy and thereby promote relapse prevention.

The opponent processes involved in the physiology and psychology of hedonic conditions are reviewed by Solomon (1980) and applied to addictions by Koob and LeMoal (1997) as well as

Kreek and Koob (1998). Physiological factors and their interrelationship with operant and Pavlovian conditioning processes as applied to MMT and detoxification are reviewed by Latowsky (1996).

A report of case study (de Vos, Ufkes, van Brussel, & van den Brink, 1996) is cited as a concluding example. An individual with a herion addiciton in MMT reported taking 500 and 600mg of methadone, respectively, on the 2 days prior to admission to the clinic. The patient showed extremely high plasma levels of methadone and yet reported highest craving during the 2 hours before and after methadone ingestion. Further investigation of the patient's serum levels was completed as well. Increased and fast metabolism of methadone was ruled out by the data. An extremely high tolerance to methadone was present. The investigators concluded conditioned withdrawal or a drug-compensatory conditioned response was likely operating to produce the craving. Patient education related to awareness and identification of anticipatory conditional responses and coping skills for their management was the recommended intervention.

Treatment Factors

Depth of processing
Reinforcement "reward and incentives" for compliance
Punishment for non-compliance

Depth of Processing

Issues related to the **etiology** of the patient's addiction are addressed from a relapse-prevention perspective. What are the factors in the patient's history that precipitated and/or maintained the addiction-based (maladaptive) behavior? Over the course of treatment, such factors will arise and should be addressed. The caveats are inherent in the modality of MMT itself: outpatient supportive services. Core issue processing must not be aimed toward, or consist of a process, that produces a crisis within the patient not safely resolvable by MMT. Crisis intervention services should not be required to "clean up the mess" created by MMT, for MMT should not precipitate that which requires crisis intervention to resolve. The goal(s) of MMT should always be kept in mind: assisting the patient in achieving/maintaining an adaptive and healthy lifestyle. As an outpatient service, MMT is not initiated in the context of involuntary psychiatric hospitalization, and does not require inpatient chemical dependency services to provide the structure required to support its patients while receiving care. Traditionally, "deep processing" psychotherapy of "deep issues" has not been a part of the MMT treatment package; empirical studies fail to support its efficacy. It has been found (Avants, Margolin, Kosten, Rounsaville, & Schottenfeld, 1998) that a lower intensity and less socially demanding day of treatment produces more abstinence during and after treatment, as well as fewer risk behaviors (compared to a high intensity, socially demanding day). One recent **meta-analysis** (Brewer, Catalano, Haggerty, Gainey, & Fleming, 1998) discussed a study finding poorer outcomes in MMT that included psychotherapy as a component, i.e. patients did worse. This single finding was not borne out by the meta-analysis itself, however.

Stress as a factor in development of addiction, and its involvement in the relapse process has been extensively studied. Kreek and Koob (1998) review the empirical and theoretical literature related to the synergism of biological and psychological factors in response to drug use, development of addiction, and both internal and external stressors as they related to precipitating and maintaining dysregulated systems related to addiction (such as neurological reward pathways and the hypothalamic-pituitary-adrenal axis). Stimulant-opioid interaction, insufficiency of methadone dose, and resulting altered psychoneuroendocrine thresholds to these stresses have been discussed as important factors in relapse prevention (Hartel, Schoenbaum, Selwyn, Kline, Davenny, Klein, & Friedland, 1995).

A recent study (Shaham, Erb, Leung, Buczek & Stewart, 1998) of cocaine- and heroin-trained rats demonstrated that a footshock stressor reliably reinstated previously extinguished cocaine- and heroin-taking behavior. This stress-induced drug taking behavior was attenuated by administration of an antagonist of the corticotropin-releasing factor receptor (CRF_1) involved in coordination of the body's stress response. The authors point out that this antagonist, CP-154,526, has been shown to: inhibit CRF-induced action in the **locus ceruleus** (where **clonidine** plays a role in symptomatic treatment of opiate withdrawal syndrome), block anxiogenic responses to startle, produce anti-depressant-like effect in learned helplessness procedures and block the stress response of CRF-induced **adrenocorticotropic hormone** (ACTH) release.

Opiate agonists have been used as a probe in exploration of the HPA axis' role in addiction, the biological psychiatry of stress in addictions (levels of ACTH and cortisol), and medication development in addiction disorders (Schluger, Ho, Borg, Porter, Maniar, Gunduz, Perret, King & Kreek, 1998). In short, their study supports previous evidence that the HPA axis is connected with the endogenous opioid system, and its stress responsivity plays a role in the neurobiology of acquisition of dependence, maintenance of use, abstinence, relapse, treatment and vulnerability for addiction. Further, Schluger et al. note that long-term methadone maintenance normalizes neuroendocrine function, including diurnal variation of the HPA axis (a contrast to heroin addiction).

Taken together, then, the avoidance of physiological and psychological withdrawal syndrome, physiological stress responses, learned helplessness-based depression spectrum mood states, anxiety-producing situations and related response sets would seem prudent in MMT. Client functioning, retention in treatment, and relapse rates would all likely improve, at least in theory (and given what research demonstrates about the role of stress in conditioning theories of addictions and relapse), if not empirically.

Reinforcement "Reward And Incentives" for Compliance

By definition, "reinforcement" means to increase the frequency of a response. Likewise, by definition, a "reinforcer" is that which produces reinforcement as an effect. What a certain individual finds reinforcing, another individual may not find reinforcing. What a certain individual finds initially reinforcing, may later not find reinforcing. Perhaps the first cookie one is offered serves as a reinforcer, while the 10^{th} cookie may seem in no way appealing. If the consequence (being given a cookie) of a behavior (clean urine sample) increases the frequency of the response (clean urine sample), then the consequence (cookie) was reinforcing, by definition. If the consequence (cookie) of a behavior (clean urine) did not increase the frequency of the response (clean urine), then the consequence (cookie) was not a reinforcer, by definition.

Various attempts have been made by researchers and clinicians at selecting and implementing reinforcers for compliance in methadone maintenance. Case studies examining the potential efficacy of primary reinforcers (e.g. food) and secondary (conditioned) reinforcers (e.g. money, tokens) have been conducted, as have large group quasi-experimental designs examining the impact of various token economies on individual cases as well as general program outcome measures. One study examined the use of conditioned reinforcers (Rowan-Szal, Joe, Hiller, and Simpson, 1997). The method used employed a card stock board displaying a matrix of patients and months, wherein the various compliance factors earned a patient a sticker for that month (the sticker being a star); stars of differing values were redeemable for food vouchers at a local grocery store. Another study employing various reinforcement schedules providing vouchers redeemable for food or services even found a significant increase in cocaine abstinence and a decrease in cocaine craving (in addition to increases in opiate abstinence) for one of the experimental conditions (Silverman, Wong, Umbricht-Schneiter, Montoya, Schuster & Preston, 1998).

Other methods have included examining the efficacy of allowing take-home bottles of medication, monetary rewards, participation with other compliant clients and staff in recreational activities/outings, and invitations to attend a congratulatory dessert. Take-home bottles reduce the demand for daily clinic attendance and treatment progress may mean less group therapy is required: these consequences may be reinforcers. One study failed to find a difference in treatment retention or relapse to heroin use after institution of a one-day-per-week clinic closure wherein every patient received a take-home bottle (Gelkopf, Bleich, Hayward & Adelson, 1998). Take-home bottles were found to successfully reinforce attendance of therapy sessions; the authors suggested using take-homes to first reinforce attendance of relapse prevention skill training, followed by making take-home approval contingent on participation in adjunct treatment services that patients may otherwise reject (Kidorf, Stitzer, Brooner & Goldberg, 1994). Remember, “negative reinforcement” means the removal of an aversive as a positive consequence for engaging in the desired behavior (like taking a client off of their loss of privileges for correcting their behavior); negative reinforcement is meant to *increase* the frequency of a response, and as such is defined as a *reinforcer, not a punisher.*

Overall, reinforcement strategies have been successful as an additional component of MMT in modifying target behaviors. These changes have been demonstrated to be both statistically and clinically significant. Methadone as a pharmaceutical is not theorized or designed to alter substance use beyond the opioid class of chemicals, and it alone can not completely restructure the patient’s lifestyle from addiction-based to self-enhancing. Reinforcement protocols can add a significant and important therapeutic component to MMT.

Punishment for Non-Compliance

By definition, “punishment” means to decrease the frequency of a response. Likewise, by definition, a “punisher” is that which produces punishment as an effect. What a certain individual finds punishing, another individual may not find punishing (or might even find reinforcing). What a certain individual finds initially punishing, may later not find punishing. Perhaps delivering the first aversive serves as a punisher, while the 10th aversive may not seem of significance. If the consequence (delivering an aversive consequence) of a behavior (dirty urine sample) decreases the frequency of the response (dirty urine sample), then the consequence (aversive) was punishing, by definition. If the consequence (aversive) of a

behavior (dirty urine) did not decrease the frequency of the response (dirty urine), then the consequence (aversive) was not a punisher, by definition. Types of punishment include: delivery of an aversive (providing a rat electric shock), time-out from positive reinforcement (separating an acting out child from their classmates), and response-cost (late fee added to a bill for past-due status).

Practices of various programs have included reducing and/or withholding the methadone dose as a punitive response to treatment non-compliance behaviors. Other strategies have included disciplinarily detoxing the patient in a 7-day withdrawal schedule.

Certain problematic clinical pictures should certainly warrant "administrative discharge" from a methadone program. In hindsight, however, perhaps some approaches to the use of punishment for non-compliance have served as a counter-intuitive and problem producing and/or maintaining reaction of the treatment system to patient symptoms. The patient in a respiratory ward is not thrown out for coughing. The schizophrenic patient is not told they will get their medication when they stop hallucinating. One would expect the patient to exhibit signs and symptoms of their problem, some of which may not neatly fall within the parameters of "compliance." If addiction is a biopsychosocial disorder, one should expect the presentation of the disorder during the treatment episode, and expect that such presentation would include psychosocial content, in addition to the biological aspects of the addiction.

As addiction is a relapsing, chronic disorder (especially for those qualifying for methadone maintenance treatment), one should realize that defense mechanisms and change-resistance are a part of the clinical picture that is the addiction. If defense and resistance are not inherently part of the disorder, how did the patient come to develop the level of addiction that is present? The argument that defense and resistance are not normally present and/or part of the disorder is counter-intuitive, speaks against clinical, empirical findings with large numbers of subjects as well as case study data, and flies in the face of the findings of the MMT field after 30 years of practice nationwide. As such, mechanistically applied punitive measures for defense/resistance strategies may be **iatrogenic**, or at least not effective and/or efficient. Perhaps the appropriate treatment response for the stabilized patient who demonstrates continued opiate use is an adequately investigated and increased methadone dose to block the potential for euphoria (rather than automatically discharging the patient for non-compliance), i.e. the serum level may not be adequate or receptor blockade has yet to occur.

Kidorf and Stitzer (1996) report on an experimental method combining reinforcement and punishment. Patients received a take-home bottle of methadone for each drug-free urine sample. For submitting a urine sample dirty for drugs, the patient was placed on a "split dose" of methadone, wherein half the daily dose was administered in the morning and the other half was administered in the afternoon of the same day (necessitating twice daily attendance of the program). The authors pointed out that this combined reinforcement/punishment contingency did not require the program to purchase or obtain supplies such as tokens, vouchers, etc. that other contingency strategies might require.

Controversies

"Substituting one drug for another"
Long-term maintenance vs. drug-free goal
High dose vs. low dose
Changes in dispensing and regulation

"Substituting One Drug For Another"

One controversy surrounding MMT is that MMT is merely "substituting one drug for another." This controversy is resolved as explained below.

Methadone is a pharmacologically pure μ agonist swallowed as a liquid, and is found to cause no tissue damage. What is often purchased as "heroin" may truly be described as "junk" and may not be as safe, regardless of the route of administration. As such, the comparison is between "apples and oranges." Kirn (1988) notes that this confusion, based on a deficient understanding of MMT, has had a negative impact on the addiction treatment field in general, and MMT programs and patients in particular.

Further, methadone maintenance therapy (MMT) consists of much more than merely prescribing methadone. By definition, MMT is an entire *blend* or package of biopsychosocial interventions: medical services (including, among other things, physical exam and on-going physician involvement and nursing support of physical health), psychiatric services/referrals and management/monitoring, addictions-specific education and counseling, group and/or individual counseling services, a family-focused therapy component, casework support aimed at assisting the patient in healthy lifestyle issues (including, among other things, occupational, recreational and family concerns), as well as positive/healthy socialization opportunities. The methadone taken, then, as a part of MMT is prescribed, dispensed and self-administered within a broad therapeutic context. As such, MMT is much more than "substituting one drug for another."

By contrast, heroin is acquired and (normally) self-administered in a psychopathologic environment or at best a psychopathogenic context.

One need not avoid pharmacotherapy as part of addictions treatment. Some would philosophically state it is "wrong" for the patient to be "dependent" upon the medication they are taking. Often, sage feedback from the collective wisdom in the recovering community is that the newcomer to recovery go to "90 meetings in 90 days." Being thus "dependent" upon the meeting is appropriate. Likewise, it need not be "wrong" as some may think for the newcomer to MMT to take "90 doses in 90 days" at the clinic. One may argue that as a patient matures in recovery, the patient may not need to attend meetings as frequently. The argument may then be extended against MMT patients via the notion that in MMT one has no choice but to daily take their methadone and thereby they are cheated out of the chance to mature. However, demonstrating readiness for the flexibility provided by "take-home" doses may resolve that apparent problem; the necessity of daily clinic attendance is obviated.

Long-Term Maintenance vs. Drug-Free Goal

Another controversy regarding MMT (that even exists within the addictions treatment field) is the long-term maintenance/drug free goal controversy. This apparent problem is resolved by individualized treatment planning strategies, as explained below.

Some hold that while on MMT, the individual is not "recovering" in the true sense, because the patient is "on drugs." As such, some reject MMT as a viable treatment option on philosophical grounds alone. This controversy (or at least confusion over definition of terms, and the integrity and goals of treatment) spills over to the entire community at large and has a negative impact on the addiction treatment field and its patients (Kirn, 1988). Kirn notes one example of such confusion is the notion that physical dependence is the same as addiction; prescribing practices then become restrictive (and inadequate) out of fear and addiction pathology continues as a result (Cooper, 1992).

Likewise, the philosophical orientation of certain methadone maintenance programs and/or practitioners within them is one of always needing to accomplish a "drug-free" (that is, methadone free) goal for all clients, and usually to do so within a pre-set limit time period. Kirn (1988) questions why someone's insulin would be stopped at a certain point in time just because their underlying disease was not being cured. D'Aunno and Vaughn (1992) in their national study of methadone clinic practices found that 50% of the units encourage their patients to detoxify after being in MMT less than 6 months, and that 54% of units have an average length of client treatment of 20 months or less. Other programs/practitioners are of the philosophy that all patients should always remain on methadone maintenance therapy for the rest of the patient's life, as a drug-free goal is not realistic or achievable.

A scientist-practitioner approach precludes a "one-approach-fits-all" method of patient treatment. Individualized treatment planning strategies are marked by the following: initial data base collection, on-going assessment of the patient across biopsychosocial factors, and on-going modification of the diagnosis/ treatment plan/prognosis as the case conceptualization and interventions are compared against treatment outcomes by examining the data. What approach is warranted by the facts of the case, and is agreed upon by the patient-physician-counselor-nurse treatment team? Perhaps the short and/or long term goals initially set by the treatment team will change over time. Neither the least nor the most intrusive/restrictive interventions should always be applied first in every case (Cooper, 1992; Kirn, 1988). Neither should be inflexibly applied against the clear facts of the case and the consensus of the treatment team, especially when both the interpretation of the facts and the consensus of the team are in agreement. The pragmatism of applying the best current scientific healthcare treatment practices is thus preferred over the semantic, philosophical, rhetorical debate within the treatment field.

The early course of change in MMT was explored in a study (Cacciola, Alterman, Rutherford, McKay & McLellan, 1998) comparing time of admission with 2 and 7 months after admission on measures of substance use and general lifestyle. Overall, significant improvements were made relatively rapidly (the 2 month measure) for all clients on measures of substance abuse and general functioning. However, the clients retained in treatment did significantly better than those who dropped out. Empirical evidence related to positive treatment outcomes as a function of length of treatment and treatment retention, indicates that for MMT a 1 year minimum treatment duration, on the average, is best (Hubbard, Craddock, Flynn, Anderson & Etheridge, 1997;

Simpson, Joe & Brown, 1997). Strain, Stitzer, Liebson and Bigelow (1993) in their study of methadone dose and outcome found that patients showed improvements over time on measures of psychosocial functioning and psychological symptoms, emphasizing the importance of non-pharmacologic aspects of MMT and the influence of treatment retention.

Latowsky (1996) reviews the literature related to the methadone detoxification as well as the interrelationship of mood and the methadone withdrawal process. He discusses factors related to deciding for or against the goal of detoxification and/or continuing long-term methadone maintenance. He also reviews factors contributing to maximizing the efficacy of the decision making process, such as valuing patient input. Among factors considered before recommending detoxification are that a significant benefit from MMT has been attained and rehabilitation criteria are met, such as vocational, social and abstinence stability. Patient characteristics including a voiced concern, showing interest, assimilation into a non-drug world, support from family and friends and absence of a detoxification phobia are positively correlated with successful detoxification. He also points out that psychotherapy as an adjunctive program component has predictive value for successful detoxification.

Adding to the difficulty of achieving successful detoxification (among those for whom it is an appropriate goal) are several factors, Latowsky contends. Higher prevalence rates of depressive spectrum disorders among opioid addicts is one of those factors. Another is the evidence for withdrawal symptomatology beyond the acute phase of detoxification. This syndrome appears to contain elements of an organic mood syndrome as well as subjective opioid withdrawal. Latowsky continues by discussing the literature related to physical neuroadaptive changes to the chronic presence of opiates as well as their absence after detoxification. These factors, as Latowsky discusses, coupled with the anxiety, or detoxification phobia found in some patients, may exacerbate withdrawal elicit escape/avoidance based behaviors in some patients, reducing the likelihood of successful detoxification and sustained post-detoxification abstinence.

High Dose vs. Low Dose

The high dose/low dose controversy is resolved by adequate dosing strategies relative to the changing goals of dosing.

Methadone maintenance consistently beats no-treatment conditions, regardless of dose; on the whole, higher doses are generally correlated with greater reductions in opiate use and (even when controlled for) treatment retention (Hartel, Schoenbaum, Selwyn, Kline, Davenny, Klein, & Friedland, 1995; Holmstrand, Änggård and Gunne, 1978; Maddux, Prihoda, & Vogtsberger, 1997; Strain, Bigelow, Liebson & Stitzer, 1999; Strain, Stitzer, Liebson & Bigelow, 1993; Strain, Stitzer, Liebson & Bigelow, 1998). However, some practitioners/programs have an *a priori* dosing bias based on a philosophical orientation/view that determines the ceiling and floor of therapeutic dose regardless of and instead of empirical investigation. Examples of such *a priori* dosing practice decisions include those “low dose programs” that view maintenance doses above 50mg/day as “wrong”, regardless of the clinical picture and the facts of each case. Another example of such *a priori* dosing practices includes “high dose programs” in which all clients are automatically maintained on doses of at least 120mg/day “because nothing less than that will work for any of our clients.” D’Aunno and Vaughn’s (1992) national study of MMT program policies and practices found that 25% of clinics set an upper limit on dose levels of 20-

60 milligrams, and that almost 25% of clinics had a majority of patients on decreasing dose levels (but were not detoxing).

The apparent controversy over dose is resolved by the principle of adequate dosing. Rather than tie methadone doses to a philosophical orientation, the physician dispenses the dose that is adequate for good treatment outcomes. Such dosing practices will neither under-medicate nor over-medicate any individual patient, but each would be stabilized on the dose appropriate for their case. A certain patient may be successfully maintained on what one might consider a "low dose" such as 35 mg for years, while another may be maintained on a "moderate" dose of 75 mg, or another on a "high" dose of 120 mg or more. The adequate dose for each patient is prescribed. A variable range of maintenance doses will be distributed across all patients in the program; the average adequate dose is merely the average.

Why prescribe doses within a certain narrow range, independent of and in contradiction to, the data pertinent to the individual case? Why ignore negative outcomes and/or positive outcomes, and continue unchanged prescribing practices, and expect or hope for positive change? Does the practitioner's mere belief about the efficacy of the methadone dose limit the upper and lower bounds within which the practitioner may prescribe? Why not prescribe the dose that works, rather than the one you believe should work, in contradiction to the data? Should program policy alone regulate the methadone doses that can be selected?

Taking the above into account, what are the goals of adequate dosing principles and practices?

Initial objectives drive toward short-term stabilization of the patient. Determination of the presence or absence of withdrawal and/or intoxication signs and symptoms is imperative. Such data provide the staff working with the patient a feedback loop about the adequacy of the methadone dose. Additionally, urine toxicology tests investigating the presence or absence of, among other things, prescribed methadone and street opiates, provide another indication of methadone dose adequacy. Is there a blockade of the euphoric effects of illicitly consumed opiates? Are *both* early subjective withdrawal symptoms and later objective withdrawal signs prevented by an adequately high dose of methadone, or should the dose be raised? Is intoxication prevented by an adequately low dose of methadone, or should the dose be lowered? Initially, the patient should be made comfortable, experiencing neither withdrawal nor intoxication; the correct methadone dose to match the level of physical/psychological dependence on the illicitly consumed opiate of the patient's addiction should be prescribed. Craving of opiates should be eliminated. These points are stressed by Hiltunen, Lafolie, Martel, Ottosson, Boreus, Beck, Borg and Hjemdahl (1995) who add the importance of development of a standardized rating scale of objective and subjective withdrawal for assistance in adequate dose determination on a patient-by-patient basis.

Maintenance strategies drive toward long-term stabilization of the patient. While the same assessments as mentioned above are continued, the correct blocking dose should be consistently determined and prescribed. The milligram level required for an adequate blocking dose may change over time, due to changes in the physical health status of the patient, other medications that may be prescribed, psychosocial/environmental changes, exposure to use cues, and relapse patterns. In general, however, long-term maintenance doses that are successful tend to be stable over time.

DePetrillo, Camara, Owen and Flockhart (1999) report on a case study of a "fast metabolizer" of methadone who showed significant objective opiate withdrawal 10-12 hours after ingesting 400 mg of methadone. The patient was eventually maintained successfully on a daily oral dose of 150 mg of methadone along with 200 mg of ketoconazole per day to slow methadone metabolism. As the authors discuss, this patient might have perhaps been regarded a treatment failure if not individually assessed and pharmacologically managed.

Changes In Dispensing and Regulation

The methadone maintenance outpatient programs in the USA have been regulated and checked for compliance primarily by the FDA (among other regulatory bodies) for the last few decades. This compliance model of program adherence to Federal standards has come under increasing scrutiny and challenge recently. The proposed changes and their potential impact are many (Parrino, 1998). One change that has been adopted is to implement a privatized credentialing model of regulation and compliance monitoring; the Substance Abuse and Mental Health Services Administration (SAMHSA) has gained oversight from the Food and Drug Administration (FDA), and delegated it to the Center for Substance Abuse Treatment (CSAT). CSAT has implemented private monitoring through healthcare accrediting bodies such as the Joint Commission for the Accreditation of Health Care Organizations (JCAHO). One proposed change is to place methadone maintenance dispensing privileges in the hands of every physician, and detach the dispensing of maintenance methadone from the context of outpatient chemical dependency treatment services and provide it in private outpatient physician offices.

Arguments against the credentialing model and its allowance of any physician to dispense methadone for maintenance treatment of those with addictions in their private office may be as follows. "Methadone maintenance therapy" by definition, is a blend of pharmacological and psychosocial interventions; MMT employs a team of qualified physician, nursing and counseling staff plus the patient. Receiving methadone is not equivalent to MMT. Rather, some of the services providing the context of the patient receiving methadone, (and help define the treatment model of MMT) include the following: individual and/or group therapy (related to relapse prevention planning, stress management training and interpersonal skills development, for example), case management assistance with accessing community resources and providing patient advocacy, and supportive nursing services.

Does dispensing methadone outside of a chemical dependency treatment context constitute MMT? Should physicians without addiction (bio-psycho-social) specific, and methadone (maintenance) specific training be allowed to prescribe and daily dispense methadone on an on-going basis for chronic narcotic dependence in their community-based private practice office? Is the public prepared to confront their own stereotypes and be exposed to the methadone maintenance patient in the physician's waiting room or office setting? Public objections (of at least some extent) to this policy would be expected. The unintended outcomes of private physician offices dispensing methadone to maintenance patients have yet to occur on a wide scale.

Why should a Federal shift to a credentialing model for MMT programs "fix" or prevent the compliance concerns noticed by the current model of license inspections? Why should privatizing the accreditation process "fix" or prevent current concerns? Why would the weaknesses of the MMT model, and its use by various practitioners/programs be eliminated or

reduced by expanding access of methadone maintenance dosing to every physician in the USA? Some would conclude that the regulation, practice and oversight of the MMT field should not be changed as stated above.

Arguments in favor of the credentialing and private physician model may be as follows. There are too few MMT treatment slots. Everyone who needs MMT should be able to get it. Stabilized patients with clean urine should not be tied to a clinic, but should merely see their doctor periodically. If they started doing poorly, they could return to the MMT clinic for counseling as indicated. MMT is a simple pharmacological modality for the stabilized patient and does not require the type and amount of federal oversight for dosing, dispensing and regulation of related clinical practices. Every physician should therefore have the option to use methadone to treat those with opiate addictions in their private practice according to medical (not regulatory) guidelines. Methadone maintenance programs will benefit from promulgation of evidence-based guidelines and best practice models, and the accountability to perform accordingly; patient treatment outcomes will improve as a result.

Efficacy

Efficacy studies: process and outcome
Methadone vs. LAAM vs. Buprenorphine vs. Naltrexone
Stereotypes of methadone maintenance patients

Efficacy Studies: Process and Outcome

MMT is the most widely studied drug addiction treatment modality, and shows the greatest efficacy across methods in the treatment of opiate addiction (Substance Abuse and Mental Health Services Administration, 1997). MMT, according to one meta-analytic study, reduces illicit opioid use in 36-73% of patients (Marsch, 1998).

Outcome measures that typically show significant improvements across studies include: extent of opiate use, executive function and activities of daily living, occupational status, extent of family dysfunction, extent of criminal behavior and legal difficulties, recreational status, physical health, medical complications from opiate use and related health-risking behaviors; extent of HIV transmission rates, involvement in education, extent of use of drugs other than opiates, extent of needle sharing, psychological/psychiatric health and/or stability, death rates, and involvement in a positive/recovery lifestyle and demonstrated ability to address on-going relapse prevention problems such as identification and management of relapse warning signs and high risk situations. It may be worth noting that immune responses may be differentially affected by opiate use (Chao, et al, 1996; Yeager, et al 1995).

Efficacy findings in MMT are robust. They have been consistently found across decades of research and clinical practice, across various research methods by many different researchers, across decades of clinical practice by large numbers of practitioners in many different clinics, as well as across continents, cultures, and sub-cultures of opiate addicted persons (Marsch, 1998; Murray, 1998).

Cacciola et al (1998) question whether treatment effects in MMT are incremental and cumulative over time, or if patients who are retained longer in treatment may differ from other patients from the outset. Although MMT is efficacious on the whole, there are patient characteristics and treatment components found to be of predictive validity for positive outcomes in MMT. Among those in MMT, who tends to have the best outcomes? Patient characteristics associated with treatment retention and/or positive outcomes include: being older, African American, on higher doses of methadone, married, and employed (Strain, Stitzer, Liebson & Bigelow, 1997). One study (Belding, McLellan, Zanis & Incmikoski, 1998), however, failed to find any patient characteristic that differentiated treatment "responders" from those that were "nonresponsive" other than extent of opiate use prior to onset of MMT (i.e., the "nonresponders" reported greater heroin and cocaine use at time of admission). Further work remains to be completed for clarification of these factors and their influence in MMT.

Variables have been identified that are predictive of continued illicit use of opiate: high levels of pre-treatment opioid use, having been in prior treatment for opiate addiction, no abstinence from opiates prior to treatment, association with substance abusing peers, high stress, short length of treatment and leaving treatment prior to completion (Brewer, Catalano, Haggerty, Gainey, & Fleming, 1998).

Methadone alone (dispensed in the absence of MMT program social services and positive social functioning in the patient population) has been shown effective in reducing heroin use when employed (Maremmani, Nardini, Zolesi & Castrogiovanni, 1994). One may ask, however, what characteristics of MMT programs and staff significantly correlate with the best outcomes? Flexible dosing practices built on guidelines for adequate dosing (Cooper, 1992; Maddux, Prihoda & Vogtsberger, 1997; Maremmani, Nardini, Zolesi & Castrogiovanni, 1994), availability of treatment retention and duration at a 1 year minimum (Hubbard, Craddock, Flynn, Anderson & Etheridge, 1997; Simpson, Joe & Brown, 1997), availability of individual and group sessions with both psychotherapy and addictions treatment components, adding a family-therapy focused treatment component (Stanton & Shadish, 1997), psychiatric services and/or firm referrals and working relationships with psychiatrists, case management services, and supportive (rather than blanket application of a generally confrontational approach) therapist style (Kang, Magura, Nwakeze, & Demsky, 1997) are factors found in enhanced MMT clinics; the clinics practicing according to such standards show the best outcomes. More recently, changes in MMT clinic practices (as a result of adopting a federal requirement for clinic accreditation) and the resulting clinical outcomes are being evaluated. One national study found JCAHO-accredited MMT programs were more likely to provide adequate methadone doses compared to the national average of non-accredited clinics, and that national efforts to improve methadone clinic practices are making progress (D'Aunno and Pollack, 2002).

Treatment efficacy is predicated on treatment retention. One study (MacGowan, Swanson, Brackbill, Rugg, Barker & Molde, 1996) examined client and program characteristics against treatment retention rates, and various treatment outcome measures as a function of treatment retention. Variables contributing to retention were: having been in MMT previously, limiting injection behavior in the first 90 days of treatment, and being older. Treatment programs built on a primary care model, rather than a 12-step or case management model retained clients best. The authors suggested that the combined components of primary healthcare, a physiological/psychological and addictions counseling approach to opiate dependence, and other (for example) vocational services related to client lifestyle, found within the primary care model account for its efficacy in retention and outcome. They also stressed the importance of

an open, objective attitude of the staff toward level of dose, and toward methadone as a medicine as a positive factor in the model's outcomes. In contrast to a case management approach, or a 12-step model, the primary care model included a three phase system of decreasing patient contact as progress is made through treatment. Suggested areas for programmatic attention and specific modifications were for increased individualization for patients that are younger and found to inject during their first 90 days of treatment.

Methadone vs. LAAM vs. Buprenorphine vs. Naltrexone

Levo-alpha-acetylmethadol hydrochloride (LAAM) is a μ agonist that is even longer acting than methadone: dosing is required approximately every 72 hours (Brandt, Cabansag, & France, 1997; O'Brien, 1997). **Buprenorphine** acts as a partial agonist at μ receptors and an antagonist at κ receptors. **Naltrexone** is an opiate antagonist.

The majority of findings demonstrate superior efficacy of methadone (MMT) over LAAM in treatment of opiate addiction (Glanz, Klawansky, McAullife, & Chalmers, 1997). This is in part due to the fact that LAAM has not been approved for opiate maintenance therapy (OMT) as long as methadone: practitioners have less experience with LAAM relative to methadone, and there are simply fewer studies. Stabilization of the LAAM patient is more difficult than with methadone due to the slower nature of the metabolism of LAAM – dose changes must be made more slowly and take longer periods of time to take effect. LAAM dose does appear to affect its efficacy, but more study is needed (Oliveto, Farren & Kosten, 1998). Some proponents of MMT suggest that the advantage of MMT is daily clinic attendance – a comfortable daily ritual further assisting in stabilization and maintenance by providing a channel for positive re-direction of addiction-type cognitions and behavioral impulses. Proponents of LAAM suggest daily clinic attendance is a disadvantage of MMT (due to inconvenience), and claim that take-home bottles of methadone do not obviate this problem. One suggestion for reducing the frequency of clinic visits in OMT is to decrease the rate of methadone (or LAAM) metabolism by concurrently prescribing ketoconazole (Grudzinskas, Woosley, Payte, Collins, Moody, Tyndale & Sellers, 1996).

Further work comparing the overall efficacy of OMT through use of methadone vs. LAAM appears needed. Would a best practice model dictate methadone be used throughout the initial stabilization period, and for several months following for rapid dose changes and compliance monitoring, then switch to LAAM long-term maintenance? Is there a sub-population that can be identified whose psychological dependence is kept better in check through daily administration, regardless of whether or not clinic attendance is required? What are the clinical indications for the selection of one over the other (LAAM or methadone)? The list of empirical questions may be long and should be researched further; more clinical practice will also help clarify the issues.

Buprenorphine (Johnson & Fudala, 1992) has not been studied nearly as extensively. It has failed, on the whole, to match or beat the efficacy of methadone in OMT. Its role in OMT (Compton, Wesson, Charuvastra, & Ling, 1996) has been extensively questioned and debated, with some hope and excitement, as it is a partial opiate agonist/antagonist. Clarification in the indications for prescribing buprenorphine and further empirical investigation in its use are needed. Head-to-head comparisons of buprenorphine with methadone and LAAM in OMT efficacy outcome studies are of questionable usefulness, as they are different classes of medication with theoretically different purposes.

Naltrexone is an opiate antagonist. Its role is clear and well researched in detoxification of physiological opiate addiction. Whether rapid or prolonged, naltrexone precipitated opiate withdrawal and detoxification has been well established. Its efficacy as a maintenance treatment for opiate addiction is not great relative to methadone. Why? Naltrexone is shorter acting than methadone and prevents euphoria from opiate administration. Therefore, it must be willingly taken by the abstinent patient, not purposefully skipped for a dose in order to achieve a high upon relapse to an opiate.

Stereotypes of Methadone Maintenance Patients

MMT patients are often stereotyped by society at large, including within the primary and mental health care treatment provider system, and even within the addiction treatment provider community (Cooper, 1992; Kang, Magura, Nwakeze, & Demsky, 1997). Opiate addiction and MMT are both often misunderstood and/or stereotyped and/or judged unfairly with a lack of information (Kirn, 1988). Terms or labels may reveal a judgmental attitude. If held by treatment service providers, such attitudes will be perceived by the patient and taint the therapeutic relationship and milieu. Treatment effectiveness is diminished as a result (MacGowan, Swanson, Brackbill, Rugg, Barker, & Molde, 1996), as is the credibility of the practitioner and the practitioner's organization; organizational policy should reflect the primacy of patient dignity (Rosenbaum, et al, 1996).

Murphy and Irwin (1992) describe three findings of their qualitative interviews and ethnographic sampling techniques. First, "identity limbo" results from MMT patients being considered "sold out to the system" by those in active addiction, "not in recovery" by those in abstinence-oriented 12-Step recovery, and still "addicted" by the uninformed lay-public. Second, this identity limbo they argue, naturally results in "concealing work". This refers to the daily "job" duties required of patients to hide MMT patient status from those that do or may judge or misjudge them. Finally, an awkward "pretense awareness" is developed where the patient and the person with whom they interact both maintain awareness that the pretense of not being an MMT patient is false, but the topic is never discussed.

Persons with opiate addictions receive enough condescension and judgement as a function of their biopsychosocial illness already. They deserve and should rightfully expect respect, compassion, and fair, top-quality treatment services in a way to protect and build their dignity.

Summary and Recommendations

SUMMARY:

The euphoric properties of opiates are subject to mitigation by conditioning and physiological factors; these factors in turn produce tolerance. Tolerance necessitates increased dosages of the opiate over time *within a specific cue context* to produce the same effect previously achieved by lower doses. Eventually, physiological and psychological dependence may develop, wherein administration of adequate doses of opiate over time is required to escape or avoid the discomfort of opiate withdrawal syndrome. Over the course of the opiate user's drug use history, the earlier motivation of pleasure seeking is replaced by the acquired motive of escape from, or avoidance of, physical and/or intra-psychic pain. Chronic opiate abuse histories typically result in intravenous administration of higher and higher quality and/or quantity street drugs or oral consumption of pharmaceuticals, with a pattern of multiple doses each day over uninterrupted time periods as long as years. **Sequelae** of such addictive disorders and the lifestyles required to support them include deep abscesses at injection sites, damage to skin, nerve fibers or blood vessels, liver dysfunction, sexually transmitted diseases, and blood-borne illnesses such as hepatitis or HIV infection, etc. Psychosocial sequelae include deterioration in employment, family system, recreation and executive function status. One approach to interrupting such a picture is methadone maintenance therapy (MMT).

Properly employed, MMT is the most successful treatment for opioid dependence. MMT is a stabilization of the disorder, not a cure. It is targeted for those severely, chronically opioid dependent individuals who can not or do not succeed in alternative treatments aiming at a drug-free goal with development of a self-help/recovery lifestyle. Properly prescribed, methadone does not make the patient “high” and it prevents the patient from becoming “sick.” The features of methadone’s action in the human body are of significant importance to understand. MMT should be delivered by an expert, experienced, multi-disciplinary team that includes the patient and possibly the patient’s family. MMT should be available on demand and on a sliding scale of cost to the patient. Methadone should be dispensed at an adequate dose to significantly reduce or eliminate illicit opioid use, and MMT should be available to a patient for an indefinitely long time period if necessary. The patient’s individual perceptual framework and experience should be explored and understood by the treatment team. Patient education regarding identification of drug use cues, responses and coping skills is necessary for relapse prevention training. Overall, reinforcement strategies are to be favored over punishment strategies. Reinforcement strategies have demonstrated efficacy in producing behavior change in use of non-opiate chemicals (not amenable to decrease by methadone dosing) and related lifestyle behaviors. Integrated or at least supportive services (psychiatric, general medical, psychotherapy, family-focused therapy, case management and patient advocacy) are important to include in MMT. Stereotypes should be identified; the ways in which staff and health care systems perpetuate and participate in them should be eliminated and replaced with efficacy-building approaches. Additional findings in research will continue, and perhaps increase our understanding of the biopsychosocial factors involved in opioid dependence disorders and their treatment (especially pharmacogenetics, psychneuroendocrinology, and new medications).

RECOMMENDATIONS FROM THE LITERATURE:

Knowledge And Skill Areas:

Specialized knowledge and skills in addictions treatment, especially relapse prevention

Accepts the basic goals and objectives of MMT as a treatment approach, and avoids the conveying of a negative attitude toward treatment and recovery with MMT

Can relate appropriately with the patient population, according to ethical guidelines, and demonstrate an empathic, non-judgmental attitude toward the patient

Specialized knowledge in theory and practice of MMT, including:

- Understands goals of adequate dosing and narcotic blockade
- Understands basic pharmacokinetics of methadone relative to licit and illicit opiates
- Knows and can recognize signs and symptoms of opiate action as well as physical and psychological withdrawal from opiates
- Knows basic drug interactions affecting metabolism of methadone
- Understands conditioning theories of addictions and applies it MMT
- Understands the altered perceptual framework found in some patients
- Understand harm reduction theory and applies it to the practice of MMT
- Recognizes the limits of MMT and correctly determines when to refer

Policy And Procedure / Program Design And Practice:

Design token economy to build on reinforcement for program compliance (esp. drug-free for drugs other than opiates)

Treatment slots should be available when needed

Reduce barriers to treatment, such as cost

Involves patient and perhaps family members as part of the treatment team

Include family therapy or family-focused therapy component

Patients should know their dose

Determine and dispense the adequate dose

No upper limit on dose based on program philosophy

No systematic time limit to begin encouraging patient withdrawal

Factors From the Literature Suggesting A Change In Methadone Dose

Consider Increasing Dose If:	Consider Decreasing Dose If:
Patient reports illicit use of opiates	Request by nurse
Opiate finding in drug toxicology monitoring	Request by counselor
Opiate craving	Request by patient
Withdrawal, objective*	Request by physician
Withdrawal, subjective*	Administrative discharge
Patient leaves ASA	Intoxication, objective*
Initial induction still underway	Intoxication, subjective*
Blockade induction not complete	Allergic reaction to methadone
Plasma methadone level not sufficient	
Internal/External stressors	
Request by physician	
Request by patient	
Request by nurse	
Request by counselor	

*Conditioning theories of addictions would suggest this may be a conditional response phenomena, not necessarily driven by current opioid use or acute physiological withdrawal.

DECISION TREES:

Stages of Treatment

1. Early Induction
2. Late Induction
   - Is blockade of euphoric effects of illicitly consumed opiates achieved?
   - Are subjective withdrawal symptoms prevented? (especially craving)
   - Are objective withdrawal symptoms prevented?
   - Is intoxication from methadone prevented?

3. Maintenance
   - MAINT. DOSING: Consider adequacy of serum level and:
   - Is illicit opiate use reduced/eliminated?
   - Physical health change impacting adequate dose?
   - Other medications that may produce interaction?
   - Psychosocial changes? (displaying relapse patterns)
   - Environmental changes? (exposure to use cues)

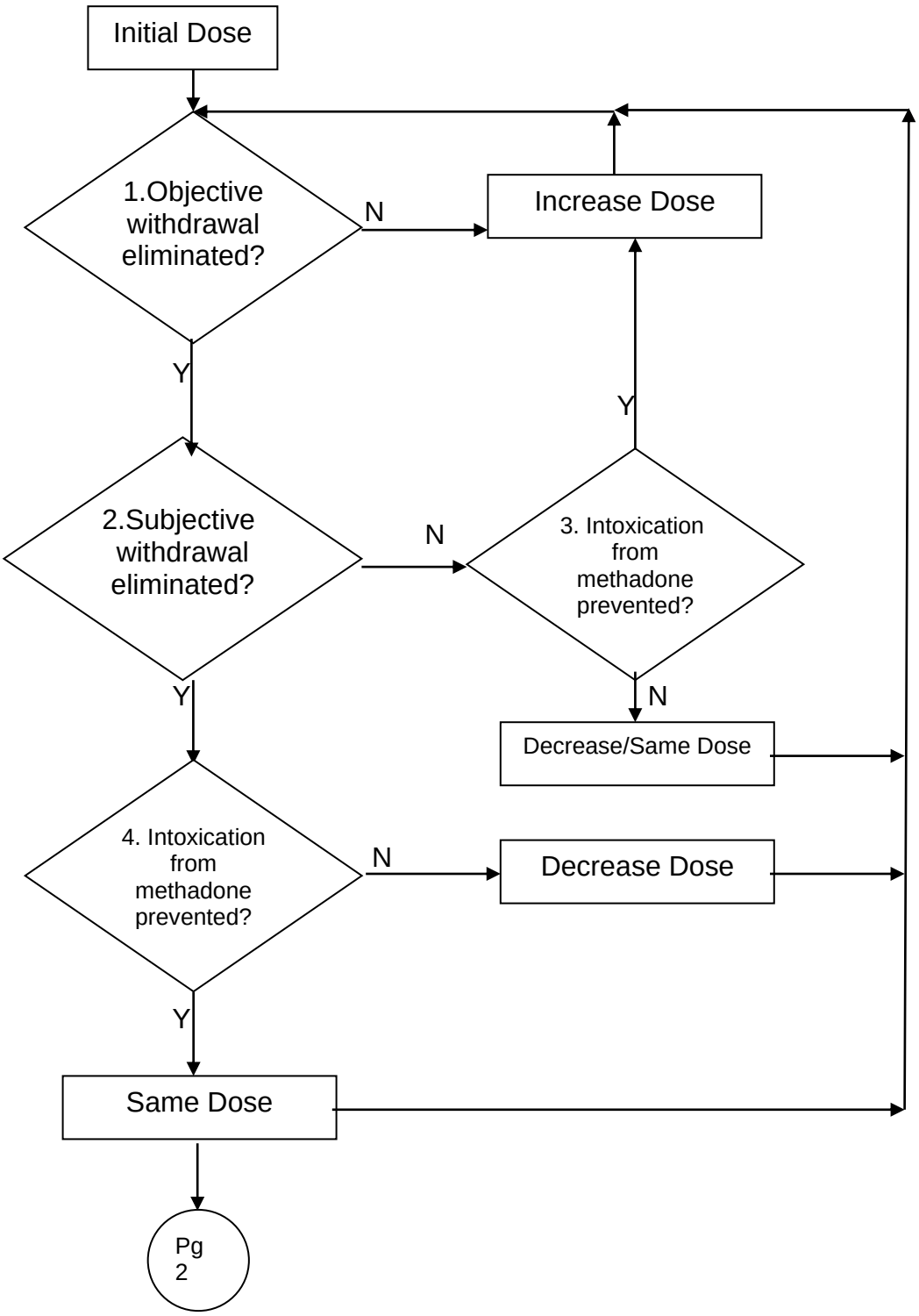
4. Medical Maintenance
   - Consider number of available treatment slots, number on waiting list, and length of time on waiting list
   - Has the patient been in MMT for a minimum of 1 continuous year?
   - Bio-psycho-social stabilization of the patient?
   - Willingness and likelihood of return to the MMT modality if indicated?
   - Likelihood of return to illicit opiate use without on-going methadone ingestion?
   - Significant benefit is being achieved?
   - Significant improvement toward meeting rehabilitation criteria (eg. vocational, social?
   - Abstinence stability?
   - Patient voices positive concern for self related to continued progress?
   - Demonstrates positive interest in on-going healthy lifestyle?
   - Assimilated into a non-drug sub-culture?
   - Support from family or friends?
   - Demonstrates knowledge and management of withdrawal phobia?

5. Voluntary & Indicated Withdrawal
   - Significant benefit achieved?
   - Rehabilitation criteria met? (e.g. vocational, social and abstinence stability)
   - Patient voices positive concern for self related to continued progress?
   - Demonstrates positive interest in on-going healthy lifestyle?
   - Assimilated into a non-drug sub-culture?
   - Support from family or friends?
   - Absence of withdrawal phobia?
   - Likelihood of continued abstinence and recovery lifestyle without on-going methadone ingestion?
   - Has the patient been in MMT for a minimum of 1 continuous year?

Methadone Maintenance Therapy (MMT)
Treatment Guidelines

Part 1: Dosing in Treatment Phases

INDUCTION DOSING



Methadone Maintenance Therapy (MMT)
Treatment Guidelines – Flowchart Text

Part 1: Dosing in Treatment Phases

INDUCTION DOSING

1. **Objective withdrawal eliminated?** Initial induction dosing aims at elimination of objective withdrawal of the patient – titrating up to a dose adequate to eliminate opiate withdrawal signs:
   A. lacrimation
   B. rhinorrhea
   C. diarrhea
   D. diaphoresis
   E. muscle cramping
   F. vomiting
   G. dilated pupils
   H. piloerection
   I. fever
   J. yawning
   K. insomnia

   Unless objective withdrawal is eliminated expeditiously, all other concerns related to the objectives of induction dosing are virtually academic, as the patient shall in all likelihood, return to the illicit use of opiates to accomplish this themselves. The treatment team will need to make a determination that withdrawal has been eliminated in order to proceed beyond this point. Once accomplished, the methadone serum level has temporarily begun to match the patient's level of physiological opioid dependence. The patient will continue to be assessed as to the on-going adequacy of the methadone dose for further prevention of physiological withdrawal signs over time.

2. **Subjective withdrawal eliminated?** The aim of dosing now moves from the primacy of importance of eliminating physiological withdrawal to the concern of subjective withdrawal. Patient comfort may be thought of as the goal of emphasis at this point in induction. Subjective withdrawal symptoms include:
   A. muscle aches
   B. joint pain
   C. "aching bones", as many patients report
   D. nausea
   E. craving opiates
   F. fear of impending physiological withdrawal

   Similarly, subjective withdrawal, if not eliminated expeditiously, shall in all likelihood prompt the patient to return to illicit opiate use to eliminate the discomfort. These symptoms are to be taken seriously by the treatment team, and dosing considerations and changes made to eliminate them all. Once accomplished, the methadone serum level has temporarily matched the patient's level of physiological and psychological opioid dependence. A caveat is that fear of impending withdrawal may be solely a withdrawal phobia in some patients, the presence of which is not alone a necessary indicator for increasing the methadone dose, as it is in these patients not tied to adequacy of serum methadone level. Alternatively, the treatment team must consider that any of these subjective states are likely to prompt illicit opioid use, and may precipitate conditioned physiological withdrawal signs, and further

destabilize the patient. Prior to increasing the methadone dose to eliminate subjective withdrawal, a further consideration must be made.

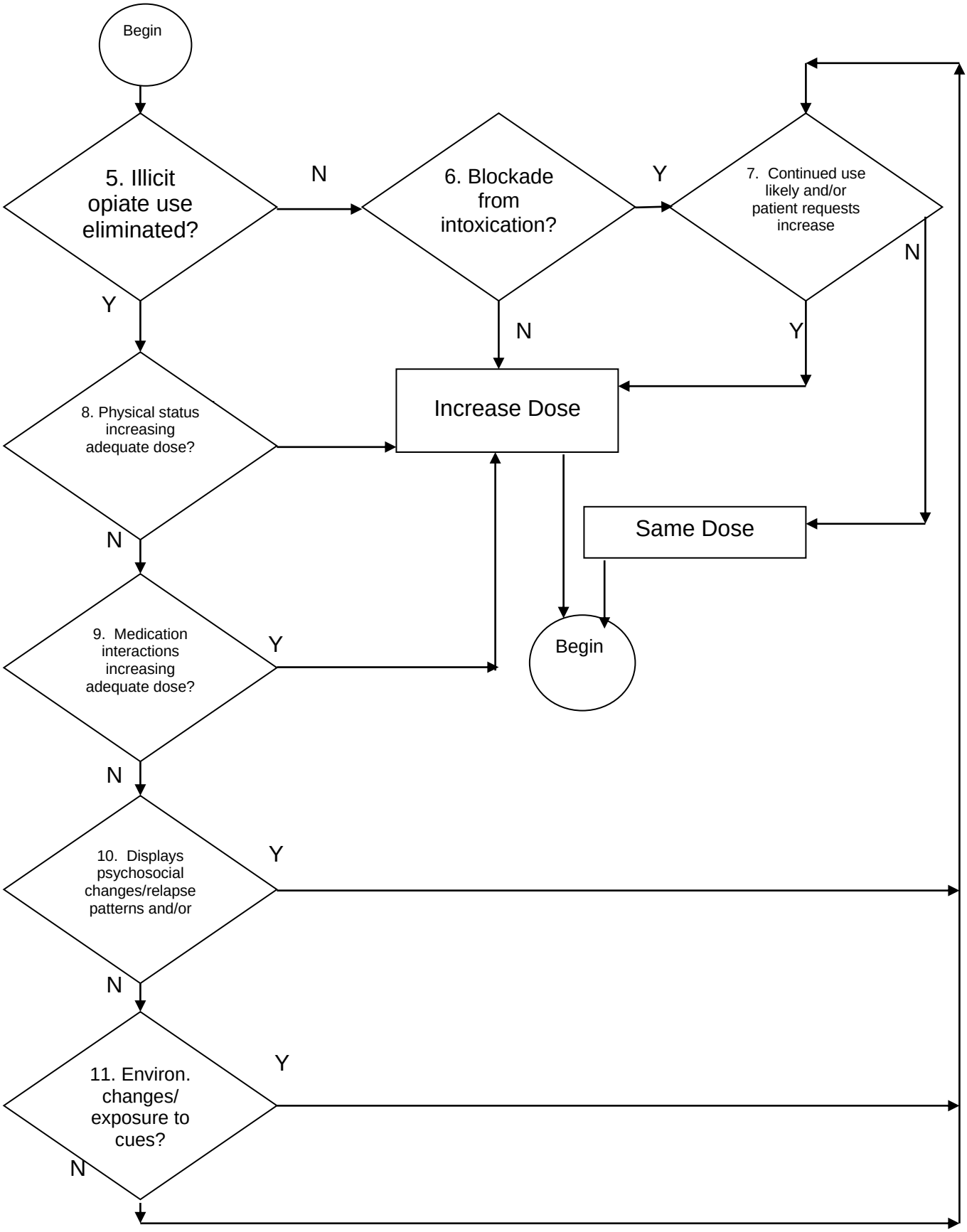
3. **Intoxication from methadone prevented?** If the subjective withdrawal has not been eliminated, the treatment team must consider this question before deciding to increase the methadone dose. As long as intoxication from methadone has been prevented, increasing the dose would appear safe. If the dose is increased, on-going assessment is indicated for continued prevention of objective withdrawal, subjective withdrawal and methadone intoxication.

   It is possible, however, that a patient report evidence of subjective withdrawal and yet display objective evidence of methadone intoxication. In such a situation, the treatment team would likely not attempt to increase the methadone dose to eliminate the subjective evidence of withdrawal. Alternatively, the treatment team would hold or reduce the methadone dose, depending on the extent of intoxication, for example. Reducing the dose may provoke objective withdrawal and illicit opiate use, while maintaining the dose may prolong methadone intoxication. As such, the patient must be further monitored and assessed for continued prevention of objective withdrawal, subjective withdrawal and methadone intoxication. Evidence of opiate intoxication (not severe) includes the following:
   A. initial euphoria
   B. later, apathy
   C. dysphoria
   D. psychomotor agitation or retardation
   E. impaired judgment
   F. pupillary constriction
   G. drowsiness (“nod”)
   H. slurred speech
   I. impaired attention or memory

4. **Intoxication from methadone prevented?** If the subjective withdrawal has been eliminated, the treatment team must consider this question before deciding to maintain the methadone dose. The aim of early induction is stabilization. Methadone intoxication in the absence of objective or subjective withdrawal would likely indicate a reduction of the methadone dose, especially to the extent the patient is over-medicated. If the methadone dose is reduced, the patient must be further monitored and assessed for on-going prevention of objective and subjective withdrawal.

   An absence of methadone intoxication, however, in the patient for whom objective and subjective withdrawal has been eliminated, indicates that the methadone dose should be held. The patient has temporarily achieved a stabilization that is the goal of initial induction. The patient must be further monitored and assessed for on-going prevention of objective or subjective withdrawal. The absence of these over time gives increasing confidence to the treatment team that early induction has been achieved.

MAINTENANCE DOSING



5) **Illicit opiate use eliminated?** Principally, opiate use should be regarded a clinical issue relevant to on-going patient assessment, goal setting and treatment planning. Illicit opiate use should not be principally regarded as a disciplinary issue of patient non-compliance. If present, opiate use constitutes one indicator of inadequate methadone dose, and ultimately inadequate serum level. Illicit opiate use is directly tied to continuation of the opiate dependence disorder and its harmful/risk-laden lifestyle. As such, a key goal of MMT is the elimination of illicit opiate use. When present, illicit opiate use may constitute a patient's attempt to determine if opiate intoxication is possible, or to experience intoxication if they know or believe it is possible.

6) **Blockade from intoxication?** A main objective of MMT, the elimination of illicit use, is more likely achieved to the extent the methadone has produced a blockade against intoxication produced by illicit opiate use. Determination of intoxication may be made by direct observation of the patient, if possible, or by interviewing the patient about the results of illicit opiate use. If illicit opiate use has occurred, and blockade has not been accomplished, an increase in methadone dose would likely be indicated.

   - Other factors contributing to illicit opiate use should be reviewed and the care plan modified accordingly. Consider factors 8-11.

7) **Continued use likely and/or patient requests increase?** Even if blockade from intoxication has been achieved, the patient should be further assessed. The patient's perception of the ability of the illicitly used opiate to provide the desired intoxicating effects should be established, as it may be tied to likelihood of further illicit opiate use as well. If the patient believes intoxication is possible or likely, regardless of accomplishing blockade, illicit use of opiate becomes more likely or perhaps probable. If the treatment team determines continued illicit use of opiate is likely, an increase in methadone dose would seem indicated. Aside from that determination, the patient may request an increase in methadone dose. Among other concerns, this would tend to indicate a significant degree of external locus of control, as well as limited coping skills, and may constitute a request for help from the patient. In any case, a request for an increase in dose from the patient should normally be honored, and an increase given.

   Alternatively, if the treatment team determines that continued illicit opiate use is not likely, and the patient is not requesting an increase in methadone dose, normally the methadone dose would be held.

8) **Physical status increasing adequate dose?** The patient's physical status may alter the adequate dose (serum) level. For example, rapid metabolism would produce different serum levels in two different patients taking the same dose. If the patient displays or reports withdrawal syndrome at what should normally be an adequate dose, continues illicit opiate use (especially in spite of dose increases), or reports intoxicating effects of illicit opiate use (especially in spite of dose increases), methadone serum level testing should be considered. Pregnancy and its resulting changes may render a previously adequate methadone dose inadequate.

- Alternatively, physical status may require a decrease to a new adequate dose. For example, compromised liver function may result in a serum level that is too high, producing intoxication. When questioned by the treatment team in a way not easily rectifiable by dose adjustments and observation, serum levels should be obtained.

9) **Medication interactions increasing adequate dose?** Pharmacist consultation would provide access to up-to-date information regarding medications and their interactions with methadone. Certain medications accelerate methadone metabolism:
   A. rifampin
   B. phenobarbital
   C. phenytoin
   D. carbamazepine

   Opioid antagonists and certain opioid agonists may promote withdrawal syndrome related to methadone. Increasing the methadone dose may be indicated to maintain an adequate serum level, given the medication interaction. Obtaining methadone serum levels may be required to make this determination.

   - Decreasing the dose to an adequate level may be required due to the reduced metabolism of methadone caused by certain medications:

   A. antifungals (e.g. ketoconazole)
   B. cimetidine.

10) **Displays psychosocial changes/relapse patterns?** The patient may evidence change in their psychosocial status or display patterns of thought, feeling, attitude or behavior that, taken as a pattern, indicate illicit opiate use is impending. Significant threats to on-going elimination of illicit use of opiate are the following:
   A. Withdrawal phobia
      i. negative expectancies
      ii. anticipatory anxiety over dose reduction
      iii. avoidance behavior
      iv. hypervigilence in monitoring withdrawal signs and symptoms
      v. interpretation of physical and mental changes as withdrawal syndrome
   B. Drug-compensatory conditional withdrawal
      i. muscle aches
      ii. joint pain
      iii. “aching bones”, as many patients report
      iv. nausea
      v. vomiting
      vi. craving opiates
      vii. fear of impending physiological withdrawal
      viii. lacrimation
      ix. rhinorrhea
      x. diarrhea
      xi. diaphoresis
      xii. muscle cramping
      xiii. dilated pupils
      xiv. piloerection
      xv. fever
      xvi. yawning

xvii. insomnia

C. Deteriorating self-efficacy
   i. patient requests an increase in methadone dose
   ii. evidences lack of skill magnitude to prevent illicit opiate use
   iii. evidences lack of skill magnitude to manage withdrawal phobia

Unless properly managed, the patient's likelihood of illicit use is greatly increased, as a result of changes in these major categories. An increase in methadone dose may be indicated to help stabilize the patient and reduce the likelihood of illicit opiate use.

11) **Environmental changes/exposure to cues?** To the extent the patient encounters external cues associated with illicit opiate use, or is involved in negative environmental change, the risk of return to illicit opiate use increases. The patient's self-help support structure may collapse for reasons separate from, and out of the control of the patient. The patient may encounter a variety of external cues that prompt conditional withdrawal syndrome, such as:

A. Visual: syringe, money, negative neighborhood
B. Auditory: phone call, music, conversation
C. Olfactory: odor of bleach, cooking heroin, propane
D. Other internal and/or external stressors

Additionally, the patient may experience increased stressors that serve as use cues. These cues may be internal or external. The members of the treatment team working with the patient must be careful to provide care that does not out-strip the patient's inner resources for self-help and on-going maintenance of a positive, drug-free lifestyle. For example, deep-processing psychotherapy may present internal cues beyond the patient's coping ability. Changes in major life areas, such as health, family relationships, financial, marital or employment status may exceed the patient's level of adaptive response. Drug-related cognitive sets and feeling/moods that move the patient toward relapse should be avoided, or resolved efficiently and effectively. An increase in methadone dose may be indicated to re-stabilize the patient and reduce the risk of a return to illicit opiate use.

Glossary

See Dox, Melloni, & Eisner (1993), Miriam-Webster (1983) and Mosby (1998) *for these terms*.

abstinence: free from drugs of abuse

adrenocorticotropic hormone (ACTH): a hormone of the anterior pituitary that, among other effects, controls the release of corticosteroids. Levels of ACTH increase in response to stress

agonist: a drug that can interact with a receptor and initiate a drug response

antagonist: a drug that, by producing no biological effects, inhibits action of another drug at a certain receptor

***a priori*:** without examination or evidence

bioavailability: the degree of activity or amount of an administered drug or other substance that becomes available for activity in the target tissue

buprenorphine: an partial opiate agonist/antagonist analgesic

carbamazepine (Tegretol): an anticonvulsant, specific analgesic for trigeminal neuralgia and mood stabilizer

clonidine: an antihypertensive; its action in the locus ceruleus mediates symptoms of opiate withdrawal

conditional response (CR): a response (very similar to an unconditional response) whose elicitation by an originally neutral stimulus is conditional upon prior pairing of that stimulus with an unconditional stimulus

conditional stimulus (CS): an originally neutral stimulus that through pairing with an unconditional stimulus has come to elicit a conditional response

dependence: physiological and/or psychological requirement for a chemical, without which the person will experience withdrawal

dynorphin: an endogenous opioid with potent analgesic effects

dysphoria: a disorder of affect characterized by depression or anguish

endogenous morphine (endorphin): a chemical produced by the body producing pharmacological effects similar to morphine

enkephalins: an endogenous neuropeptide depressing neurons in the CNS, inhibiting neurotransmitters for pain perception, also reducing the emotional impact of pain; may be involved in the development of psychopathologic behavior

ethyl alcohol: beverage alcohol

etiology: study of factors involved in the development of an illness

euphoria: the state of feeling well-being or elation

extinction: in Pavlovian conditioning the decrease of a response by repeated presentation of a cue; in operant conditioning the decrease of a response by repeated withholding of a reinforcement of a behavior previously rewarded

extinguished: in Pavlovian conditioning the absence of elicitation of a conditional response to a conditional stimulus, derived from repeated presentation of the conditional stimulus; in operant conditioning the absence of a previously rewarded behavior by the witholding of the reward

half-life: time necessary to reduce the plasma value to half its initial value

homeostasis: constancy in the internal environment of the body naturally maintained by adaptive responses promoting healthy survival

hypervigilence: nervous heightened awareness and scanning of the external environment

iatrogenic: condition caused by treatment or diagnostic procedures

ketoconazole: an antifungal medication

levo-alpha-acetylmethadol hydrochloride (LAAM): a synthetic opiate agonist used in opiate maintenance therapy

ligands: a cross-reactant molecule attached to a cell surface

locus ceruleus: a group of neurons in the floor of the fourth ventricle; a part of a major norepinephrine pathway of the central nervous system.

meta-analysis: a systematic method of evaluating statistical data based on results of several independent studies of the same problem

methadone: a synthetic opiate agonist used in pain control or for opiate detoxification or maintenance therapy

naltrexone: an opiate antagonist

narcotic analgesics: chemicals derived from opium or synthetically that alter perception of pain, induce euphoria, mood changes, induce sleep, mental clouding, depress cough and respiration, constrict pupils and nausea – prolonged use can produce physical and psychological dependence

ng/ml: nanogram per milliliter

opiate: any narcotic analgesic

pentazocine (Talwin): an agonist/antagonist narcotic analgesic

pharmacokinetics: study of action of a drug within the body, including and mechanisms of absorption, distribution, excretion and metabolism and duration of effect

phenytoin (Dilantin): an anticonvulsant medication

physiological dependence: the state of one who physically requires a drug to avoid physical (and perhaps additionally psychological) withdrawal

psychological dependence: the state of one who psychologically requires a drug to avoid psychological withdrawal

psychophysics: the branch of psychology concerned with relationships between physical stimuli and sensory responses

psychotomimetic: a drug whose effects mimic the symptoms of psychosis

receptor site: a location on a cell surface where certain molecules, such as neurotransmitters, attach to interact with cellular components

rifampin: an antibacterial drug

saliency: degree of noticeability

sequelae: an abnormal condition that follows and is the result of a disease or injury

serum: the clear, thin, sticky part of the blood containing no blood cells or platelets

sign: objective finding perceived by an examiner, such as a fever or rash

symptom: subjective indication perceived by the patient

tolerance: increased resistance to a drug that the body develops in response to repeated exposure to the drug

unconditional response (UCR): the reflexive (smooth muscle) response of the body, such as salivation to an unconditional stimulus, such as food

unconditional stimulus (UCS): a cue (such as food) that unconditionally produces a reflexive response of the body, through survival-level neurological hard-wires

vasomotor: pertaining to modulation of the autonomic nervous system, such as blood pressure and cardiac function

withdrawal: physical and psychological response to abrupt cessation of administration of a chemical upon which one is dependent and to which one is tolerant

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Suggested Links of Interest

American Methadone Treatment Association
http://www.aatod.org

American Psychiatric Association's Practice Guidelines on Substance Use Disorders
http://www.psych.org/clin_res/pg_substance.html (discontinued, 2nd ed due 2006)

Addiction Treatment Forum (free methadone newsletter) Home Page
http://www.atforum.com

American Society of Addiction Medicine
http://www.asam.org

Center for Opioid Research and Design
http://www.opioid.umn.edu

Chemistry of Opioid Analgesics
http://www.acsmedchem.org/module/opioid.html

Federal Methadone Regulations
http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=2001_register&docid=01-723-filed

"How Methadone Works": Jocelyn Woods of the National Alliance of Methadone Advocates
http://www.methadone.org/namadocuments/es05basic_pharmacology_1.html

Mary Jeanne Kreek's Homepage
http://www.rockefeller.edu/labheads/kreek/kreek-lab.html

The Lindesmith Center, Drug Policy Research Institute
http://www.lindesmith.org/

Methadone Anonymous
http://www.methadone-anonymous.org/

Methadone Information Exchange
http://ewestp.home.mindspring.com/

Methadone Today – Methadone Newsletter
http://www.methadonetoday.org/

National Alliance of Methadone Advocates
http://www.methadone.org/

National Institute on Drug Abuse
http://www.nida.nih.gov/

NIH Consensus Statement on Effective Medical Treatment of Opiate Addiction
http://consensus.nih.gov/1997/1998TreatOpiateAddiction108html.htm

National Library of Medicine's 941 Citations on Effective Medical Treatment of Heroin Addiction
http://www.nlm.nih.gov/archive/20040829/pubs/cbm/heroin_addiction.html

Office of National Drug Control Policy Document on Opioid Maintenance Treatment
http://www.whitehousedrugpolicy.gov/publications/factsht/methadone/index.html

Opioid Analgesic Medicinal Neurochemistry Information
http://holivo.pharmacy.uiowa.edu/morphine/morphine.html

J. Thomas Payte's Homepage
http://www.jtpayte.com/

Photo of Methadone
http://www.prevlink.org/getthefacts/webphotoalbums/prescription/pages/methad3_gif.htm

Provider Directory for Methadone Maintenance Treatment
http://www.mindspring.com/~methinfex/directory/index.html

Robert Rescorla's Homepage
http://psych.upenn.edu/~rescorla/

Shepard Siegel's Homepage
http://www.science.mcmaster.ca/Psychology/ss.html

Stigma of Narcotic Addiction and Methadone
http://www.druglibrary.org/schaffer/heroin/methadone/dont/dole_nys.htm

University of Pennsylvania's (Charles O'Brien) Drug Abuse Library
http://www.med.upenn.edu/recovery/pros/library.html

Overview by SAMHSA/CSAT/OPAT on MMT Federal Regulation Changes
http://dpt.samhsa.gov/regulation.htm

