STATE OF MICHIGAN

Medication Assisted Treatment Guidelines for Opioid Use Disorders

MAT Work Group

R. Corey Waller MD, MS

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This document was developed to be a consolidated, short form set of updated, evidence-based guidelines for the treatment of opioid use disorders. Prior to starting the manuscript, current relevant guidelines were reviewed. These included, but were not limited to, the World Health Organization Guidelines, the Baltimore Buprenorphine guidelines, the Vermont Buprenorphine Guidelines, the Australian Ministry of Health Methadone Guidelines as well as the Canadian Department of Health Guidelines for use of Methadone and Buprenorphine. All National Institutes of Drug Addiction (NIDA) as well as SAMHSA materials were used in the initial review. Once this was done all information was updated to current as of April 2014. R. Corey Waller MD, MS was the primary author with Shelley Virva LMSW having authored most of the General Behavioral Health Section. The material was then reviewed by the Medication Assisted Treatment workgroup as directed by Lisa Miller (Michigan Department of Community Health) and suggested changes were incorporated. This document was not meant to be an exhaustive philosophical or theoretical journey about treatment beliefs, but rather a consolidation of current evidence that can guide the treatment, safety, efficacy and payment models driving the treatment of opioid use disorders moving forward.

I. Introduction

Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological and social manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.[1]

Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.[2]

In 2011, 4.2 million Americans aged 12 or older (or 1.6 percent) had used heroin at least once in their lives. It is estimated that about 23 percent of individuals who use heroin become dependent on it. Total US societal costs of prescription opioid abuse were estimated at $55.7 billion in 2007 (USD in 2009). Workplace costs accounted for $25.6 billion (46%), health care costs accounted for $25.0 billion (45%), and criminal justice costs accounted for $5.1 billion (9%). Workplace costs were driven by lost earnings from premature death ($11.2 billion) and reduced compensation/lost employment ($7.9 billion). Health care costs consisted primarily of excess medical and prescription costs ($23.7 billion). Criminal justice costs were largely comprised of correctional facility ($2.3 billion) and police costs ($1.5 billion). For each one of these costs there is a human being attached. Each of these is potentially made more stable and less expensive through appropriate identification, detoxification, acute treatment and recovery. The goal of these guidelines was to develop an evidence-based cohesive and consistent approach to the patient diagnosed with an opioid use disorder.

A variety of effective treatments are available for Opioid Use Disorders (OUDs). Treatment tends to be more effective when opioid use is identified early. The treatments that follow vary depending on the individual, but methadone and buprenorphine have a proven record of success for people addicted to heroin or prescription opioids. Other pharmaceutical approaches, such as behavioral therapies also are used for treating OUDs. When these therapies are used in conjunction patient outcomes are superior.

Methadone treatment has been used for more than 30 years to effectively and safely treat opioid addiction. Properly prescribed, methadone is not intoxicating or sedating, and its effects do not interfere with ordinary activities such as driving a car. The medication is taken orally and it suppresses opioid withdrawal for 24 to 36 hours. Patients are able to perceive pain and have emotional reactions. Most important, methadone relieves the craving, a major reason for relapse, associated with Opioid Use Disorders. It is also been shown that the quality of life in patients on methadone maintenance treatment is significantly improved. [3] Among methadone patients, it has been found that normal street doses of heroin are ineffective at producing euphoria, thus making the use of heroin more easily extinguishable.[4]

Buprenorphine is a particularly attractive treatment for Opioid Use Disorders because, compared with other medications, such as methadone, it causes weaker opiate effects and is less likely to cause overdose problems.[5] it is a partial agonist at the mu opioid receptor which allows for a decreased overall increase in dopamine release thus creating a ceiling effect of the addictive potential of the medication. Buprenorphine also produces a lower level of physical dependence, so patients who discontinue the medication generally have fewer withdrawal symptoms than do those who stop taking methadone. Because of these advantages, buprenorphine is appropriate for use in a wider variety of treatment settings than other currently available medications. Several other medications with potential for treating heroin overdose or addiction are currently under investigation by NIDA.[6, 7]

Naloxone and naltrexone are medications that also block the effects of morphine, heroin, and other opioids. As antagonists, they are especially useful as antidotes. Naltrexone has long-lasting effects, ranging from 1 to 3 days, depending on the dose. The injectable version of naltrexone (Vivitrol*) lasts for 30 days. Naltrexone blocks the pleasurable effects of heroin and is useful in treating some highly motivated individuals. Naltrexone has also been found to be successful in preventing relapse by former opioid addicts released from prison on probation.[8, 9]

Although behavioral and pharmacologic treatments can be extremely useful when employed alone, science has taught us that integrating both types of treatments will ultimately be the most effective approach. There are many effective behavioral treatments available for Opioid Use Disorders. These can include residential and outpatient approaches. An important task is to match the best treatment approach to meet the particular needs of the patient. Moreover, several new behavioral therapies, such as contingency management therapy and cognitive-behavioral interventions, show particular promise as treatments for patients with Opioid Use Disorders, especially when applied in concert with pharmacotherapies. Contingency management therapy uses a voucher-based system, where patients earn "points" based on negative drug tests, which they can exchange for items that encourage healthy living. Cognitive-behavioral interventions are designed to help modify the patient's expectations and behaviors related to drug use, and to increase skills in coping with various life stressors.[10] Both behavioral and pharmacological treatments help to restore a degree of normalcy to brain function and behavior, with increased employment rates and lower risk of HIV and other diseases and criminal behavior.

In addition to methadone and buprenorphine, other drugs aimed at reducing the severity of the withdrawal symptoms can be prescribed. Clonidine is of some benefit but its use is limited due to side effects of sedation and hypotension. Lofexidine, a centrally acting alpha-2 adrenergic agonist, was launched in 1992 specifically for symptomatic relief in patients undergoing opiate withdrawal.

These guidelines are intended to be read by those involved in providing psychosocially assisted pharmacological treatments at any level. The targeted readership falls into three broad groups:

- Policy makers and administrators who make decisions on the availability of medicines and the structure and funding of services in countries or in subnational health administrative regions
- Managers and clinical leaders responsible for the organization of specific health-care services, and for the clinical care those services provide
- Health-care workers treating patients within the health-care system.[11]

It is important to understand the difference between standards and guidelines. Standards are regarded as generally accepted principles of patient management. Standards are based on a synthesis of current literature and a high level of consensus among the Guideline Advisory Committee. Standards are differentiated from Guidelines in that they refer to clinical practices that potentially relate to patient morbidity and mortality and to community safety. Standards may be modified only under exceptional circumstances and where the reasons for departures from the standards are clearly documented. [12]Guidelines are systematically developed recommendations and educational references that assist the clinical provider in making clinical decisions about patient care. Clinical guidelines are recommendations that are supported by a synthesis of current literature and clinical consensus. Guidelines may be adopted, modified, or rejected according to clinical needs, individual patient considerations, local resources, and physician discretion. Guidelines do not establish inflexible protocols for patient care nor are they meant to replace the professional judgment of physicians.[12]

Prescription-opioid users often have pain problems and obtain their opioids legally from a prescriber indicating that they were still under medical supervision for their pain; these patients are more likely to have psychiatric treatment and take sedatives/anxiolytics or antidepressants[13]. This presents an especially refractory group of patients as there are no guidelines for the treatment of pain in the patient who also has an opioid use disorder. These guidelines will not attempt to make recommendations

related to these patients but will touch on appropriate screening methodology to determine who would be a good versus a bad candidate for an opioid pain medication.

Opioid Replacement Therapy (ORT) is based on a harm reduction philosophy and represents one component of a continuum of treatment approaches for opioid-dependent individuals. Opioid replacement therapy is a substitution therapy that allows a return-to-normal physiological, psychological and societal functioning. It is one possible treatment for opioid dependence. For some people, opioid replacement therapy may continue for life, while others may be able to eventually discontinue opioid replacement therapy and remain abstinent while preserving the normal level of function they attained while on opioid replacement therapy. [14]Each patient must be assessed, treated, and monitored on an individual basis. Successful outcomes through ORT require knowledge, experience, vigilance, and diligence on the part of the clinical provider, the patient, and all of those involved in treatment. Medication alone does not constitute effective treatment of opioid dependency. Effective opioid replacement therapy services should comprise all of the components enabling a clinician to live up to the standards of care as presented by the American Society of Addiction Medicine (ASAM).[15]

II. Standards of Care for the Physician Treating Substance-Related and Addictive Disorders

This Standards document was prepared by the American Society of Addiction Medicine's (ASAM) Practice Improvement and Performance Measures Action Group (PIPMAG) Standards and Outcomes of Care Expert Panel.

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George Woody, MD
David Mee-Lee, MD
Stephen A. Wyatt, DO
Patty Pade, MD
John Femino, MD

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Introduction

Background and Purpose of Standards:

The Standards of Care for the Addiction Specialist Physician (The Standards) address the unique responsibilities borne by a physician who manages or oversees the care of a patient with addiction and related disorders. They are intended to support quality improvement activities conducted by health care provider systems, health care quality entities, medical specialty certification boards, and by individual

physicians monitoring their own performance in their own practices. The Standards apply to any physician assuming the responsibility for caring for addiction and related disorders and acting in this capacity even if such a physician does not hold specialty certification in addiction medicine or addiction psychiatry. The Standards address expected physician competencies and actions with the ultimate purpose of improving patient outcomes. ASAM anticipates that The Standards will "raise the bar" of expectations and accountabilities in describing what physicians are expected to do at different points in the addiction care process. This document is a dynamic statement on quality medical care and is subject to ongoing review; it may be revised by the American Society of Addiction Medicine (ASAM) in the future based on input from ASAM leaders and consultation with other organizations that have reviewed and chosen to endorse these Standards.

It is important to note The Standards outline a minimum standard of physician performance and should not be construed as describing the extent or totality of care that a person with addiction might require. Additionally, these standards are not substance-, behavior - or setting-specific, but apply generally to the treatment of individuals with addiction involving any addictive substance or behavior – including nicotine, alcohol, prescription or illicit drugs, and/or addictive behavior such as gambling – in any medical setting. ASAM recognizes that, at this point in time, the epidemiology of addiction and the expert consensus on how best to treat addictive disorders is more firmly established in the case of substance use disorders than in the case of conditions involving addictive behaviors. Hence, the wording of The Standards primarily focuses on substance-related conditions and not addiction involving addictive behaviors. As scientific knowledge and clinical experience grow with respect to addiction not involving the use of substances, we expect that future statements about standards of care for addiction specialist physicians will be able to address evaluation, management, and care coordination for addiction more broadly.

The Standards were developed using a consensus process. Their development was overseen by a Steering Committee comprised of representatives of the key addiction physician specialty societies as well as academicians, researchers and clinicians experienced in standards development. The Steering Committee appointed an expert panel that was charged with developing the Standards document. The Steering Committee also appointed an expert panel to develop another document addressing the domains of performance measures for addiction specialist physicians, deriving from The Standards in the current document; members of the expert panel on performance measures also provided input that improved the final wording of these Standards. Along with the expert panels, a field review panel offered additional expert feedback into the making of this document. The individuals comprising the Steering Committee, the Standards Panel, Performance Measures Expert Panel and Field Review Panel are listed at the beginning of this document. ASAM is grateful for the generous support of SAMHSA, NIDA and NIAAA which made this important initiative possible.

Addiction Specialist Physicians and Professionalism Expectations:

Addiction specialist physicians include addiction medicine physicians and addiction psychiatrists who hold either a board certification in addiction medicine from the American Board of Addiction Medicine (ABAM), a subspecialty board certification in addiction psychiatry from the American Board of Psychiatry and Neurology (ABPN), a subspecialty board certification in addiction medicine from the American Osteopathic Association (AOA), or certification in addiction medicine from the American Society of Addition Medicine (ASAM).

Addiction specialist physicians should maintain their licensure to practice medicine and their certification as addiction specialists. This includes remaining current regarding clinical advances,

participating in regular self-assessment and demonstrating that, through participation in a plan of lifelong learning and practice improvement, they are actively engaged in the maintenance of their specialized clinical knowledge and competencies commensurate with a complex and ever-changing field.

The addiction specialist physician upholds the ethics policies of his/her addiction specialty organization. The addiction specialist physician also upholds the professional expectations of all physicians but has some unique professional expectations including the following:

- keeping abreast of changes in laws regarding illegal substances, the prescribing of controlled substances, criminalization of behaviors associated with substance use, clinical alternatives to criminal prosecution and incarceration, and interfaces between the health care system and the criminal justice system, including community corrections;
- understanding and complying with all applicable federal, state, and local regulations related to patient confidentiality; and
- obtaining informed consent and ensuring that patients understand the extent and limits of privacy protections.

The addiction specialist physician should be able to deal with substance use disorders as well as concurrent problems that exacerbate or arise from the patient's addiction. The addiction specialist physician should also have a good understanding of local cultures and subcultures and what local resources are available to support the patient's recovery. Ultimately, a patient's care should be oriented toward overall functioning and well-being while mitigating risk factors for substance related harm or relapse. The Standards identify what addiction specialist physicians do as they perform their clinical and administrative roles, not simply what knowledge, skills, or competencies they possess.

Addiction Specialist Physician Leadership:

The Standards presented in this document are statements of what physicians should do in their clinical practices and as the physician manifests leadership within health care teams and broader systems of care. Addiction is a complex disease that impacts many aspects of a person's life and requires long-term, coordinated care by a team of providers who can address the myriad physical, mental, social, economic, and legal ramifications of the disease. As a leader of this care team, the addiction specialist physician is well-poised to coordinate and provide the treatment required by persons with addiction due to his or her advanced and unique understanding of the dynamics of addiction and the dynamics of recovery, and how addiction manifests in varied medical, social, economic, and legal ways.

An addiction specialist physician functions at different levels of leadership or influence and as a part of formal and informal teams. As of this writing, we recognize that addiction treatment is not well integrated into most health systems and the addiction specialist physician workforce is inadequate to address individually the number of patients with addiction. As a result, collaborative management is necessary and the addiction specialist physician has a responsibility to be the leader within health care systems and/or their communities when addiction is present as part of the patient's overall clinical situation. Part of this responsibility is to help other providers and health care administrators understand how addiction affects the evaluation and management of other illnesses so that appropriate treatment is provided. This responsibility will also require that addiction specialist physicians be directly involved in quality assurance and evaluation, safety management, and professional development regarding treatment of patients with addiction within the relevant systems of care where they practice. Addiction

specialist physician leadership will also require that s/he teach new generations of clinicians in their practice settings and/or through involvement in their professional societies.

Implications and Next Steps**:**

Addiction treatment is in the process of evolving from a largely non-medical, isolated field into a more integrated part of mainstream medical care. As this occurs, new working relationships, treatment protocols, and reimbursement mechanisms will need to be negotiated, and some growing pains will be inevitable. For example, current commercial and regulatory requirements for physicians sometimes ask them to authenticate care for patients they have never seen. This threatens high quality care and can undermine physicians' decision-making. In the midst of changes and pressures both old and new, The Standards set forth here outline what we can and should expect from addiction specialist physicians in the treatment of individuals with substance use and substance-related disorders, and they can serve as a benchmark for physicians, payers, policymakers and patients alike as they seek to provide, pay for, regulate, and receive the highest quality care.

Given the evolution of the health care environment and the role of addiction treatment and addiction specialist physicians, it is expected that The Standards will be reviewed periodically and updated to reflect scientific and clinical advances in treatment and changes in the health care delivery system. ASAM invites other addiction specialty physician organizations to endorse these standards so that they will apply to as broad a physician audience as possible. The next step in this process will involve the Steering Committee overseeing the work of an expert panel as it develops a set of performance measures based on The Standards.

Standards

I. Assessment and Diagnosis

Assessment of a patient with a substance use disorder is an ongoing process. A complete assessment is a critical aspect of patient engagement and treatment planning and should be conducted during the initial phase of treatment. However, it is important to note that it does not necessarily need to be conducted at the initial visit. In certain practice situations, but especially in emergency situations, brief, focused assessments may be appropriate, but comprehensive treatment of addiction requires comprehensive assessment at some point in time; one of the competencies of an addiction specialist physician is to discern when a brief assessment versus a comprehensive assessment is needed. The addiction specialist physician is the professional most able to determine the appropriateness of medications used for addiction, and data collection and analysis must be done with the indications for pharmacological therapy and various psychosocial therapies in mind. Appropriate assessment includes data from clinical interviews, physical examination, and diagnostic procedures, to assure optimal clinical outcomes, patient safety, treatment adherence, and the appropriate stewardship of health care resources.

Standard I.1 Comprehensive Assessment: The addiction specialist physician assures that an initial comprehensive, multicomponent assessment is performed for each patient, either by performing it her/himself or by assuring it is conducted in full or in part by another qualified professional within the system in which she/he is working. The addiction specialist physician assures that, for every patient under his or her care, the assessment is reviewed and updated on a regular basis, including at every care transition, to promote treatment engagement and meet the patient's needs and preferences. A comprehensive assessment for a person with addiction includes the following components:

- *a physical exam;*
- *medical and psychiatric history;*
- *a detailed past and present substance use history, including assessment of withdrawal potential;*
- *a history of the pathological pursuit of reward or relief through engagement in addictive behaviors, such as gambling or exercise;*
- *substance use disorder and addictive disorder treatment history and response to previous treatment, including history of use of pharmacotherapies and response to such interventions;*
- *family medical, psychiatric, substance use, addictive behavior and addiction treatment history;*
- *allergies;*
- *current medications;*
- *social history;*
- *consultation with appropriate collateral sources of information;*
- *a summary of the patient's readiness to engage in treatment, potential to continue unhealthy use or return to unhealthy engagement in substance use or addictive behaviors, and the recovery environment that can support or impede recovery*
- *diagnostic formulation(s);*
- *and identification of facilitators and barriers to treatment engagement including patient motivational level and recovery environment.*

Standard I.2 Monitoring Diagnostic Procedures: The addiction specialist physician collects appropriate data from diagnostic procedures such as structured rating scales and relevant laboratory and imaging studies at baseline, and then periodically monitors these indicators as clinically appropriate.

Standard 1.3 Making the Diagnosis: Having assimilated data from interview/examination of the patient and other sources, the addiction specialist physician makes the diagnosis that guides the care of the patient, including any necessary withdrawal management services.

II. Withdrawal Management

Withdrawal management, when indicated, is a critical part of substance use disorder treatment. However, it is important to note that withdrawal management alone does not constitute adequate treatment for addictive disease and should be linked with ongoing treatment for substance use disorders. The addiction specialist physician assesses the extent to which withdrawal management is needed for specific classes of drugs. Additionally, medical decision-making by the addiction specialist physician includes determining whether, for a patient in acute withdrawal, the indicated intervention is acute management of the withdrawal syndrome or induction into agonist, partial agonist, or antagonist maintenance therapy. Thus, if the patient is to be placed on ongoing treatment with an agonist or partial agonist, then he or she should not be placed on a withdrawal regimen for that class of drugs, though other withdrawal management interventions may be indicated for other classes of drugs.

Standard II.1 Assessing Withdrawal Management Needs: The addiction specialist physician assesses the need for patient withdrawal management, the intensity of withdrawal management services needed, and the appropriate treatment environment, given the patient's severity of symptomatology. This assessment includes the number and classes of drugs from which the patient needs withdrawal management, if any, and the eventual treatment modality in which the patient will engage after the acute withdrawal syndrome has stabilized through bio-psycho-social interventions.

Standard II.2 Providing Intoxication/Withdrawal Medical Interventions: The addiction specialist physician uses validated, objective measurements of intoxication and withdrawal (when such an instrument exists for the given substance). The addiction specialist physician also pays careful attention to potential general medical and psychiatric complications during withdrawal management of a person with a substance use disorder. The addiction specialist physician documents medical decision-making and appropriate treatment planning, including appropriate level of care, for a patient undergoing withdrawal management.

- *When withdrawal management medications are indicated, the addiction specialist physician uses an evidence-supported approach to select a pharmacological agent, dosage, and route of administration.*

Standard II.3 Assuring Intoxication/ Withdrawal Psychosocial Interventions: The addiction specialist physician assures that validated psychosocial interventions are instituted concurrently with medical interventions (by him/herself or other members of the treatment team) during intoxication management and withdrawal management and provides or supervises ongoing treatment for the patient's associated substance use disorder.

III. **Treatment Planning**

The addiction specialist physician's unique training provides an understanding of the many physical, psychological and social consequences and complications of substance use disorders and recognition that influential social networks, including families, are important to the patient's treatment. The standards in this section describe the addiction specialist physicians' role in developing the treatment plan including how they would involve other referring providers, social support networks and the documentation of clinical decisions.

*Standard III.*1 *Coordinating Medical Care: The addiction specialist physician integrates and coordinates the treatment of addiction and associated problems and conditions, and negotiates with other providers the aspects of care relevant to the patient's addiction. The addiction specialist physician may be the direct provider of care, but even when he/she is only managing the direct care of other providers, the addiction specialist physician is ultimately responsible for addiction-related medical decision-making.*

Standard III.2 Providing Therapeutic Alternatives: The addiction specialist physician discusses and offers all available clinically indicated psychosocial and pharmacological therapies to all patients, assisting the patient to collaborate in clinical decision-making, assuring that the patient is aware of therapeutic alternatives. This will include the advantages and disadvantages of medications for addiction, taking into consideration cost, availability, and potential for diversion. When pharmacotherapies are part of the treatment plan, the addiction specialist physician decides with the patient about the setting for treatment, assuring appropriate dosage and duration for the medication, monitors adherence, and assures psychosocial therapies occur throughout the treatment process.

Standard III.3 Evaluating Safety: The addiction specialist physician uses his or her unique expertise to evaluate safety risks associated with the patient's substance use disorder and assures that the treatment plan addresses those risks.

Standard III.4 Addressing Comorbidity: The addiction specialist physician assures that all psychiatric and medical comorbidities are addressed concurrently rather than sequentially when concurrent treatment is clinically feasible.

Standard III.5 Involving Social Support Networks: The addiction specialist physician assures that attempts are made to involve social networks and the people therein in the treatment process. For example, the addiction specialist physician assures that appropriate support services are made available for patients' families.

Standard III.6 Documenting Clinical Decisions: The addiction specialist physician assures that the reasoning behind clinical decision-making is documented within the treatment plan in the patient's health record. Documentation in the patient's health record by the addiction specialist physician or another member of the treatment team should reflect knowledge of the patient, include options discussed and patient preferences, set out a mutually agreed-upon plan of action to accommodate the individual needs of the patient, as well as delineate measureable goals of treatment.

IV. Treatment Management

Treatment management typically refers to activities by addiction specialist physicians to assure the quality of care when addiction specialist physicians are not directly providing treatment but are managing the direct care of other providers. The standards in this section, however, also include the addiction specialists' responsibilities, if they are practicing in settings where they are directly providing care.

Standard IV.1 Assuring Quality of Care: When the direct treatment is provided by other clinicians under his/her supervision, the addiction specialist physician remains actively engaged with the monitoring and supervision of care and in providing oversight for the quality of care of the patient. This oversight includes assuring that all clinically indicated psychosocial and pharmacological therapies are discussed with and offered to all patients. When pharmacotherapies are part of the treatment plan, the addiction specialist physician decides with the patient about the setting for treatment, assuring appropriate dosage and duration for the medication, monitors adherence, and assures psychosocial therapies occur throughout the treatment process.

- *When the addiction specialist physician is managing the care rather than serving as the direct provider of care, Standards III.2-III.6 must still be followed.*

Standard IV.2 Determining Clinical Progress: The addiction specialist physician meets with the patient or assures that other clinician (s) meet with the patient to regularly assess progress toward mutually agreed-upon, measureable goals in the treatment plan.

- *If the patient and addiction specialist physician agree that progress toward these goals is adequate, then plans will be made to build upon these achievements, which may include transition to other services for recovery focused strategies.*
- *If the patient or the addiction specialist physician perceives that progress is not being made toward agreed-upon goals, the patient and addiction specialist physician will reassess the diagnosis, treatment modalities, treatment intensity and treatment goals in order to revise the treatment plan. Lack of treatment progress should lead to treatment plan revisions and not result in an inappropriate termination of care.*

Standard IV.3 Assuring Support Service Referral: The addiction specialist physician assures that the treatment plan includes referral to indicated social services.

V. Care Transitions and Care Coordination

Collaborative care is a key attribute of high-quality care and it is the responsibility of the addiction specialist physician who directly provides specialty care or supervises and manages specialty care provided by other clinicians. As of the writing of this document, complying with privacy and confidentiality laws and regulations presents challenges to addiction specialty care and general medical care providers and systems who strive to attain the goals of collaboration. Challenges notwithstanding, the physician is in a unique role to advocate for collaboration that ideally includes multiple professionals, individual patients, and family members, and to assist patients as they maneuver through often-complex multicomponent systems of care.

Standard V.1 Coordinating Treatment and Confidentiality: The addiction specialist physician takes steps to coordinate addiction care, communicates with other treatment providers and, when necessary, adjusts the treatment plan whenever patients experience a major change in physical or psychological health. This coordination is of particular importance when medications are being used to support recovery, as issues of cost, availability, potential for diversion and what to do in the event of a relapse make safe and appropriate prescription of the necessary medications challenging for those without specialized training. The addiction specialist physician also assures that proper authorizations for release of information are obtained.

- *If the patient asserts their privilege to not permit sharing of confidential addiction treatment information with other providers, the addiction specialist physician educates the patient about the health and safety risks inherent in poorly coordinated care.*

Standard V.2 Assuring Quality in Transitions: The addiction specialist physician assures that transitions between levels of care for substance use disorders are informed by a biopsychosocial evaluation, patient preferences, and the patient's history of responses to previous attempts at treatment.

Standard V.3 Sharing Information and Protecting Privacy: During care transitions, the addiction specialist physician directs that information is shared with subsequent providers about the patient's health status, current treatment plan, treatment adherence and treatment progress. The addiction specialist physician assures that proper authorizations for release of information are obtained.

- *If the patient asserts their privilege to not permit sharing of confidential addiction treatment information with other providers, the addiction specialist physician educates the patient about the health and safety risks inherent in poorly coordinated care.*

Standard V.4 Providing Referral: When patients transition from a given level of care, terminate addiction treatment, or terminate with a specific addiction provider, the addiction specialist physician provides recommendations and referrals for continuing professional care and/or self-management. The addiction specialist physician assures that the community and medical resources available to the patient, including the resources available through the patient's primary care provider or medical home, have been identified in a way that maximizes the patient's sustained functional recovery and is aligned with the patient's goals.

VI. Continuing Care Management

Continuing care management is provided when the patient has achieved stable sobriety, achieved most or met all treatment goals and the patient is ready for sustainable recovery-focused self-care. Recovery check-ups by addiction specialist physicians, just as those by primary care physicians or other providers, may promote sustained recovery and prevent relapse.

Standard VI.1 Assuring Continuity in Addiction Care: The addiction specialist physician encourages patients to meet with him or herself or with a designated care provider who intermittently monitors and assesses the patient's maintenance of recovery. The addiction specialist physician's or other care provider's assessment for continuing care management can include the following:

- *Patient and collateral interview*
- *Physical and/or psychological examination as appropriate*
- *Structured rating scales*

- *Review of current medications*
- *Laboratory studies*
- *Engagement in recovery activities*

III. Performance Measures

The development of robust performance measures and outcome measures is key to tracking how well a system is developed and how well any treatment facility or single physician performs their job. Without robust performance measures and outcome measures the true value cannot be calculated for the service rendered for the patient.

Performance measures can pertain to any level of the treatment continuum. This includes the federal government, the state government, the payer, the physician, an advanced practice provider or any other clinical professional delivering care to the patient. Below I will list performance measures that pertain to state governments, payers and the clinical provider. I will also give outcomes, which would help provide an appropriate indicator of value.

Developing and/or choosing a performance measure should be based on a number of criteria. The criteria chosen to develop and adopt the following performance measures was a combination of the overall importance of this performance happening as it pertains to adherence to guidelines or standards, the feasibility of consistently and accurately measuring the performance indicated, the possible unintended consequences if implemented, how quickly it can become actionable and how easily it would fit into already developed workflows.

Measuring outcomes attributable to performance helps to identify whether or not the performance measure does impact outcome and also allows for an indication of whether or not a given task has added value to the patient's, to the payer or to the provider of the service.

Payer (State Government/Community Mental Health):

Performance measures:

1. Does the state/CMH have all evidence-based medications available on the formulary without undue restrictions
2. Does the state/CMH provide all evidence-based behavioral therapies without undue restrictions
3. Does the state/CMH meet federal parity laws in attempting to obtain medications or therapy

related to the treatment of addiction

Outcome measures:

1. Total cost of care including social services, criminal justice expenses as well as medical expenses as compared to the national benchmark
2. Number of people obtaining treatment for opioid use disorders as compared to the per capita national benchmark

Provider:

Performance Measures:

1. For every patient receiving treatment is there a complete diagnosis including all modifiers
2. Is the patient able to see a prescribing provider within three days of discharge from the detoxification event or transfer from an inpatient or incarceration event
3. Percentage of patients with a diagnosis of an opioid use disorder on medication assisted treatment

Outcome measures:

1. Readmission rate to a higher level of treatment
2. Emergency Department utilization rate
3. Percentage of urine drug screens that are negative for another opioid

IV. Screening

A. Screening Brief Intervention and Referral to Treatment (SBIRT)

SBIRT is an early intervention approach that targets those with nondependent but potentially risky substance use to provide effective strategies for intervention prior to the need for more extensive or specialized treatment. This approach is in contrast with the primary focus of specialized treatment of individuals with more severe substance use, or those who have met the criteria for diagnosis of a Substance Use Disorder.[16] recent data has shown that this may not be terribly useful in the primary care setting however may be very helpful in the emergency department or hospital-based setting.

B. Opioid Risk Tool (ORT)

Early awareness of aberrant medication-taking behavior and subsequent physician action could disrupt behavioral patterns of medication misuse and addiction, and improve treatment outcomes. The ORT is an office-based tool designed to predict the probability of a patient displaying aberrant behaviors when prescribed opioids for chronic pain. It assesses patients for family and personal history of alcohol; illegal drug and prescription substance abuse; age; history of preadolescent sexual abuse; and specific mental disorders. Each risk factor is weighted and attributed a point value believed to reflect its risk relative to the other risk factors. The ORT has high sensitivity and specificity for determining patients at risk for opioid-related aberrant medication-taking behavior. [17]

C. Current Opioid Misuse Measure (COMM)

Clinicians recognize the importance of monitoring aberrant medication-related behaviors of chronic pain patients being prescribed opioid therapy. The COMM is a brief (17 items), self-report measure

of current aberrant drug-related behavior, and may serve as a useful tool for those providers who need to document their patients' continued compliance and appropriate use of opioids for pain. The COMM is designed to address ongoing medication misuse by asking patients to describe how they are currently using their medication. Each question asks the relative frequency of a thought or behavior over the past 30 days from "0 = never" to "4 = very often." Thoughts or behaviors asked about include, "How often have you had trouble with thinking clearly or had memory problems?", "How often have you been in an argument?", "How often have you been worried about how you are handling your medications?", and "How often have you taken your medications different from how they are prescribed?" The scale uses a low cut-off score in order to over-identify misuse, rather than to mislabel someone as responsible when they are not; thus, this scale will result in false positives, however the authors believe it is better to identify patients who have only a possibility of misuse than to fail to identify those who are actually actively abusing their medication. Ideally, the results of the COMM can serve as an educational tool for patients and providers, and should not be used to deny care but rather to make appropriate decisions about the best ways to manage chronic pain.[18]

D. Drug Abuse Screening Test (DAST)

The DAST was designed to provide a brief instrument for clinical and non-clinical screening to detect drug abuse or dependence disorders. It is most useful in settings in which seeking treatment for drug use problems is not the patient's stated goal. The DAST provides a quantitative index of the severity of problems related to drug abuse other than alcohol. DAST scores are highly diagnostic with respect to a DSM diagnosis of psychoactive drug dependence. The DAST is available in both 20-item and 10-item formats; an Adolescent version is also available. [19, 20]

In addition, the DAST provides a general measure of lifetime problem severity that can be used to

guide further inquiry into drug-related problems and to help determine treatment intensity. It takes about 5 minutes to administer the DAST-20 and 2 minutes to score the DAST-10. [20]

The DAST-10 was selected in 2012 by a group of researchers from the National Drug Abuse Treatment Clinical Trials Network (CTN) to serve as the recommended assessment tool for use in general medical settings. [21]

E. Addiction Severity Index (ASI)

The ASI is probably the most widely used standardized instrument in the field. It can be used for different purposes in assessing substance abuse clients: a) to assess the problem severity of the interviewee and b) for periodic repeated administrations to monitor and quantify change in problems commonly associated with substance abuse.

The ASI is a semi-structured interview designed to address seven potential problem areas in substance abusing patients: medical status, employment and support, drug use, alcohol use, legal status, family/social status, and psychiatric status. In one hour, a skilled interviewer can gather information on recent (past 30 days) and lifetime problems in all of the problem areas. The ASI consists of 200 items in 7 subscales. It is available in three different formats: pencil-and-paper self-administered, clinician interview, or computer-based. It takes approximately 50 minutes to 1 hour to administer. Follow-up interviews take 15-20 minutes.[22-26]

The ASI provides an overview of problems related to substance, rather than focusing on any single area. In clinical settings, it has been used extensively for treatment planning and outcome evaluation (packages for individual programs or for treatment systems are available), as it identifies problem areas in need of targeted intervention. Additionally, researchers have used the ASI for a wide variety of clinical outcome studies.

V. ASAM Definition of Addiction:

Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Addiction affects neurotransmission and interactions within reward structures of the brain, including the nucleus accumbens, anterior cingulate cortex, basal forebrain and amygdala, such that motivational hierarchies are altered and addictive behaviors, which may or may not include alcohol and other drug use, supplant healthy, self-care related behaviors. Addiction also affects neurotransmission and interactions between cortical and hippocampal circuits and brain reward structures, such that the memory of previous exposures to rewards (such as food, sex, alcohol and other drugs) leads to a biological and behavioral response to external cues, in turn triggering craving and/or engagement in addictive behaviors.

The neurobiology of addiction encompasses more than the neurochemistry of reward.[1] The frontal cortex of the brain and underlying white matter connections between the frontal cortex and circuits of reward, motivation and memory are fundamental in the manifestations of altered impulse control, altered judgment, and the dysfunctional pursuit of rewards (which is often experienced by the affected person as a desire to "be normal") seen in addiction--despite cumulative adverse consequences experienced from engagement in substance use and other addictive behaviors. The frontal lobes are important in inhibiting impulsivity and in assisting individuals to appropriately delay gratification. When persons with addiction manifest problems in deferring gratification, there is a neurological locus of these problems in the frontal cortex. Frontal lobe morphology, connectivity and functioning are still in the process of maturation during adolescence and young adulthood, and early exposure to substance use is another significant factor in the development of addiction. Many neuroscientists believe that

developmental morphology is the basis that makes early-life exposure to substances such an important factor.

Genetic factors account for about half of the likelihood that an individual will develop addiction. Environmental factors interact with the person's biology and affect the extent to which genetic factors exert their influence. Resiliencies the individual acquires (through parenting or later life experiences) can affect the extent to which genetic predispositions lead to the behavioral and other manifestations of addiction. Culture also plays a role in how addiction becomes actualized in persons with biological vulnerabilities to the development of addiction.

Other factors that can contribute to the appearance of addiction, leading to its characteristic bio-psycho-socio-spiritual manifestations, include:

a. The presence of an underlying biological deficit in the function of reward circuits, such that drugs and behaviors which enhance reward function are preferred and sought as reinforcers;
b. The repeated engagement in drug use or other addictive behaviors, causing neuroadaptation in motivational circuitry leading to impaired control over further drug use or engagement in addictive behaviors;
c. Cognitive and affective distortions, which impair perceptions and compromise the ability to deal with feelings, resulting in significant self-deception;
d. Disruption of healthy social supports and problems in interpersonal relationships which impact the development or impact of resiliencies;
e. Exposure to trauma or stressors that overwhelm an individual's coping abilities;
f. Distortion in meaning, purpose and values that guide attitudes, thinking and behavior;
g. Distortions in a person's connection with self, with others and with the transcendent (referred

to as God by many, the Higher Power by 12-steps groups, or higher consciousness by others); and

h. The presence of co-occurring psychiatric disorders in persons who engage in substance use or other addictive behaviors.

Addiction is characterized by:

a. Inability to consistently abstain;
b. Impairment in behavioral control;
c. Craving; or increased "hunger" for drugs or rewarding experiences;
d. Diminished recognition of significant problems with one's behaviors and interpersonal relationships; and
e. A dysfunctional emotional response.

The power of external cues to trigger craving and drug use, as well as to increase the frequency of engagement in other potentially addictive behaviors, is also a characteristic of addiction, with the hippocampus being important in memory of previous euphoric or dysphoric experiences, and the amygdala being important in having motivation concentrate on selecting behaviors associated with these past experiences.

Although some experts believe that the difference between those who have addiction, and those who do not, is the quantity or frequency of alcohol/drug use, engagement in addictive behaviors (such as gambling or spending)[3], or exposure to other external rewards (such as food or sex), a characteristic aspect of addiction is the qualitative way in which the individual responds to such exposures, stressors and environmental cues. A particularly pathological aspect of the way that persons with addiction

pursue substance use or external rewards is that preoccupation with, obsession with and/or pursuit of rewards (e.g., alcohol and other drug use) persist despite the accumulation of adverse consequences. These manifestations can occur compulsively or impulsively, as a reflection of impaired control.

Persistent risk and/or recurrence of relapse, after periods of abstinence, is another fundamental feature of addiction. This can be triggered by exposure to rewarding substances and behaviors, by exposure to environmental cues to use, and by exposure to emotional stressors that trigger heightened activity in brain stress circuits.[4]

In addiction there is a significant impairment in executive functioning, which manifests in problems with perception, learning, impulse control, compulsivity, and judgment. People with addiction often manifest a lower readiness to change their dysfunctional behaviors despite mounting concerns expressed by significant others in their lives; and display an apparent lack of appreciation of the magnitude of cumulative problems and complications. The still developing frontal lobes of adolescents may both compound these deficits in executive functioning and predispose youngsters to engage in "high risk" behaviors, including engaging in alcohol or other drug use. The profound drive or craving to use substances or engage in apparently rewarding behaviors, which is seen in many patients with addiction, underscores the compulsive or avolitional aspect of this disease. This is the connection with "powerlessness" over addiction and "unmanageability" of life, as is described in the first step of 12 Steps programs.

Addiction is more than a behavioral disorder. Features of addiction include aspects of a person's behaviors, cognitions, emotions, and interactions with others, including a person's ability to relate to members of their family, to members of their community, to their own psychological state, and to things

that transcend their daily experience.

Behavioral manifestations and complications of addiction, primarily due to impaired control, can include:

a. Excessive use and/or engagement in addictive behaviors, at higher frequencies and/or quantities than the person intended, often associated with a persistent desire for and unsuccessful attempts at behavioral control;
b. Excessive time lost in substance use or recovering from the effects of substance use and/or engagement in addictive behaviors, with significant adverse impact on social and occupational functioning (e.g. the development of interpersonal relationship problems or the neglect of responsibilities at home, school or work);
c. Continued use and/or engagement in addictive behaviors, despite the presence of persistent or recurrent physical or psychological problems which may have been caused or exacerbated by substance use and/or related addictive behaviors;
d. A narrowing of the behavioral repertoire focusing on rewards that are part of addiction; and
e. An apparent lack of ability and/or readiness to take consistent, ameliorative action despite recognition of problems.

Cognitive changes in addiction can include:

a. Preoccupation with substance use;
b. Altered evaluations of the relative benefits and detriments associated with drugs or rewarding behaviors; and
c. The inaccurate belief that problems experienced in one's life are attributable to other causes rather than being a predictable consequence of addiction.

Emotional changes in addiction can include:

a. Increased anxiety, dysphoria and emotional pain;
b. Increased sensitivity to stressors associated with the recruitment of brain stress systems, such that "things seem more stressful" as a result; and
c. Difficulty in identifying feelings, distinguishing between feelings and the bodily sensations of emotional arousal, and describing feelings to other people (sometimes referred to as alexithymia).

The emotional aspects of addiction are quite complex. Some persons use alcohol or other drugs or pathologically pursue other rewards because they are seeking "positive reinforcement" or the creation of a positive emotional state ("euphoria"). Others pursue substance use or other rewards because they have experienced relief from negative emotional states ("dysphoria"), which constitutes "negative reinforcement" Beyond the initial experiences of reward and relief, there is a dysfunctional emotional state present in most cases of addiction that is associated with the persistence of engagement with addictive behaviors. The state of addiction is not the same as the state of intoxication. When anyone experiences mild intoxication through the use of alcohol or other drugs, or when one engages non-pathologically in potentially addictive behaviors such as gambling or eating, one may experience a "high", felt as a "positive" emotional state associated with increased dopamine and opioid peptide activity in reward circuits. After such an experience, there is a neurochemical rebound, in which the reward function does not simply revert to baseline, but often drops below the original levels. This is usually not consciously perceptible by the individual and is not necessarily associated with functional impairments.

Over time, repeated experiences with substance use or addictive behaviors are not associated with ever

increasing reward circuit activity and are not as subjectively rewarding. Once a person experiences withdrawal from drug use or comparable behaviors, there is an anxious, agitated, dysphoric and labile emotional experience, related to suboptimal reward and the recruitment of brain and hormonal stress systems, which is associated with withdrawal from virtually all pharmacological classes of addictive drugs. While tolerance develops to the "high," tolerance does not develop to the emotional "low" associated with the cycle of intoxication and withdrawal. Thus, in addiction, persons repeatedly attempt to create a "high"--but what they mostly experience is a deeper and deeper "low." While anyone may "want" to get "high", those with addiction feel a "need" to use the addictive substance or engage in the addictive behavior in order to try to resolve their dysphoric emotional state or their physiological symptoms of withdrawal. Persons with addiction compulsively use even though it may not make them feel good, in some cases long after the pursuit of "rewards" is not actually pleasurable.[5] Although people from any culture may choose to "get high" from one or another activity, it is important to appreciate that addiction is not solely a function of choice. Simply put, addiction is not a desired condition.

As addiction is a chronic disease, periods of relapse, which may interrupt spans of remission, are a common feature of addiction. It is also important to recognize that return to drug use or pathological pursuit of rewards is not inevitable. Clinical interventions can be quite effective in altering the course of addiction. Close monitoring of the behaviors of the individual and contingency management, sometimes including behavioral consequences for relapse behaviors, can contribute to positive clinical outcomes. Engagement in health promotion activities which promote personal responsibility and accountability, connection with others, and personal growth also contribute to recovery. It is important to recognize that addiction can cause disability or premature death, especially when left untreated or treated inadequately.

The qualitative ways in which the brain and behavior respond to drug exposure and engagement in addictive behaviors are different at later stages of addiction than in earlier stages, indicating progression, which may not be overtly apparent. As is the case with other chronic diseases, the condition must be monitored and managed over time to:

a. Decrease the frequency and intensity of relapses
b. Sustain periods of remission; and
c. Optimize the person's level of functioning during periods of remission.

In some cases of addiction, medication management can improve treatment outcomes. In most cases of addiction, the integration of psychosocial rehabilitation and ongoing care with evidence-based pharmacological therapy provides the best results. Chronic disease management is important for minimization of episodes of relapse and their impact. Treatment of addiction saves lives.

Addiction professionals and persons in recovery know the hope that is found in recovery. Recovery is available even to persons who may not at first be able to perceive this hope, especially when the focus is on linking the health consequences to the disease of addiction. As in other health conditions, self-management, with mutual support, is very important in recovery from addiction. Peer support such as that found in various "self-help" activities is beneficial in optimizing health status and functional outcomes in recovery.

Recovery from addiction is best achieved through a combination of self-management, mutual support, and professional care provided by trained and certified professionals.[1]

VI. DSM-V diagnostic Criteria for Opioid Use Disorder

Substance use disorder in DSM-5 combines the DSM-IV categories of substance abuse and substance dependence into a single disorder measured on a continuum from mild to severe. Each specific substance (other than caffeine, which cannot be diagnosed as a substance use disorder) is addressed as a separate use disorder (e.g., alcohol use disorder, stimulant use disorder, etc.), but nearly all substances are diagnosed based on the same overarching criteria. In this overarching disorder, the criteria have not only been combined, but strengthened. Whereas a diagnosis of substance abuse previously required only one symptom, mild substance use disorder in DSM-5 requires two to three symptoms from a list of 11. Drug craving will be added to the list, and problems with law enforcement will be eliminated because of cultural considerations that make the criteria difficult to apply internationally.

In DSM-IV, the distinction between abuse and dependence was based on the concept of abuse as a mild or early phase and dependence as the more severe manifestation. In practice, the abuse criteria were sometimes quite severe. The revised substance use disorder, a single diagnosis, will better match the symptoms that patients experience.

Additionally, the diagnosis of dependence caused much confusion. Most people link dependence with "addiction" when in fact dependence can be a normal body response to a substance. (APA)

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12 month period:

A. Impaired control of the substance

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.

B. Social impairment

5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effect of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.

C. Risky use of substance

8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

D. Pharmacological criteria

10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of an opioid.
11. Withdrawal, as manifested by either of the following:
    a. The characteristic opioid withdrawal syndrome (refer to criteria A and B of the criteria set

for opioid withdrawal, pp.547-547 of DSM-5).

b. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.

Specify if:

In early remission: After full criteria for opioid use disorder were previously met, none of the criteria for opioid use disorder have been met for at least three months but for less than 12 months (with the exception that criterion a four, "Craving, or a strong desire were urged to use," may be met).

In sustained remission: After full criteria for opioid use disorder were previously met, now the criteria for opioid use disorder have been met at any time during a period of 12 months or longer parentheses with the exception that criterion 84, "Craving, or a strong desire or urge to use opioids," may be met).

Specify if:

On maintenance therapy: This additional specifier is used if the individual is taking a prescribed agonist medication such as methadone or buprenorphine and none of the criteria for opioid use disorder have been met for that class of medication (except tolerance to, or withdrawal from, the agonist). This category also applies to those individuals being maintained on a partial agonist, and agonist/antagonist, or a full antagonist such as oral naltrexone or depot naltrexone.

In a controlled environment: This additional specifier is used if the individual is in an environment where access to opioids is restricted (such a hospital or jail).

Coding based on current severity: Note for ICD–10-CM codes: if an opioid intoxication, opioid withdrawal, or another opioid induced mental disorder is also present, do not use the codes

below for opioid use disorder. Instead the comorbid opioid use disorder is indicated in the fourth character of the opioid induced disorder code (see the coding note for opioid intoxication, opioid withdrawal, or a specific opioid induced mental disorder). For only the opioid induced depressive disorder code is given, with the fourth character indicating whether the comorbid opioid use disorder is mild, moderate, or severe: F11.14 for mild opioid use disorder with opioid induced depressive disorder or F11.24 for a moderate or severe opioid use disorder with opioid induced depressive disorder.[2]

i. Specify current severity:

1. 305.50 (F11.10) MILD: presence of 2-3 symptoms.
2. 304.00 (F11.20) Moderate: presence of 4-5 symptoms.
3. 304.00 (F11.20) Severe: Presence of six or more symptoms.

VII. Culture of Addiction

The culture of addiction is a difficult concept to understand for those who have not directly experienced it or treated many patients who lived it. This culture has five overriding themes including escapism, instant gratification, using chemicals to emotionally cope and the seeking of otherwise unfound elation leading to superhuman stimulation of the reward pathway. However, the most common and most underrepresented emotion eventually felt is guilt. This is not an emotion portrayed by Hollywood, thought about by a jury or most importantly understood by a medical provider.

Most patients with the disease of addiction started their utilization of substances between the ages of 12 and 15. A number of patients had their first drink, their first joint or their first cigarette between these ages. Use of opioids is not far behind. For many this will merely be a passing curiosity, but for those with a genetic predisposition for addiction this can become a haunting lifelong torment. We now know that many adolescents are just trying to cover up or chemically cope with early life physical or emotional trauma. When a patient with a genetic predisposition for addiction first tries a substance, it provides escapism from the reality of their life, the pain of a relationship or the fears of an adolescent. The at-risk patients will also find that it significantly alleviates the thoughts of inadequacy or the fear of interaction, while significantly increasing confidence. While these are the perception of the person using the drug they are rarely the perceptions of those interacting with the drug user.

Once use of the drug is habituated, the patient begins to create a new normal. One that is unattainable without the drug. This new normal is the requirement for instant gratification, whether it be pain relief, anxiety abatement, fear cessation or the dissolution of sadness. By the shear nature of the disease itself one becomes separated from those people that do not use and their life that did not include a substance. They do not comprehend the untenable thirst and hunger for the dopamine their brain seeks. This separation from the nondrug using society pushes them to those that also use, perpetuating

the positive reinforcement for continued drug use, the guilt bestowed on them by the drug dealer for not having the money to buy the drug is soon followed by enticing them with one more freebie. Chasing the initial elation felt from the first high is frequently refer to as “chasing the dragon”.

In this cycle these patients will experience the highest of highs and the lowest of lows within their emotional pendulum. The thrill of thinking about going to the place where you obtain the drug in many ways equals the high they get once they take the drug. The drug induced illusion of freedom from authority, responsibilities or need to answer for anything they do perpetuates the behavior. Using seemingly innocuous medications such as Phenergan, dextromethorphan, cyclobenzaprine, pregabalin and quetiapine to “boost” the effects of any other intoxicant when money or connections run low. The desire to obtain the next “stabilizing” dose eliminates all risk assessment capability and allows the patient’s to make a seemingly “logical” decision to steal from their friend, a family member or a stranger. The now bent logic of the addicted brain drives them to make connections between cause and effect that are neither accurate nor repeatable. The use of a minor pain as a reason for buying heroin or using marijuana for their “chronic anxiety” or to help sleep after 3 days of cocaine use is “logical”. This is commonly when the emotion of guilt takes over. Medicating away the quilt and withdrawal becomes the only life focus. By the time an addict reaches this point there is no family, friend or activity that is not related to obtaining and using the drug.

People generally believed that this is a disease of the poor. However, the disease of addiction knows no socioeconomic boundaries. What one fails to recognize is that many of the patients with the untreated disease of addiction may at one time have used their education to the fullest, managed all of their daily endeavors and inhabited all points of the socioeconomic strata. But, as described above, the ever downward spiraling culture of untreated addiction has a final common pathway of either poverty or premature death.

VIII. General Pharmacological Approach

The general pharmacological approach starts very early in the treatment of any patient utilizing opioids on a consistent basis. Utilizing standardized tools for identification and measurement of the severity of the physiological signs of withdrawal is where we should start. The clinical opioid withdrawal scale (COWS) can be used to determine whether or not a patient is having significant opioid withdrawal.[27] The initial management of this withdrawal, as well as, any detoxification which is planned should use medications such as clonidine, benzodiazepines, anti-nausea medication and other medications which may help to mitigate some of the significant psychological stressors occurring with opioid withdrawal. Given that withdrawal from opioids can be completely mitigated by the utilization of medications such as methadone or buprenorphine it is advisable to determine which pathway the patient will be following for long-term treatment. The induction of either methadone or buprenorphine can be done during this acute withdrawal/detox phase. Once the patient is induced on medications and the behavioral symptoms of addiction have been abated by dose titration the maintenance phase of dosing can begin. The maintenance phase, while utilizing behavioral health input, should be addressed using the lowest amount of medications that helps to abate the behaviors associated with an opioid use disorder. Once a patient has maintained an extended period of time in remission a discussion with the patient can be had about the possibility of tapering these medications. Any taper should be done with significant patient input as the anxiety and possible withdrawal associated with taper are significant risks for relapse.[28-30]

The management of withdrawal from opioid-based medications is rather straightforward. The vast majority of symptoms are secondary to a significant amount of excitatory output from the locus coeruleus.[31-33] Given that most of these can be blocked by clonidine, the utilization of this medication is paramount. [34-38] An extensive discussion of risks benefits and alternatives to the

patient should be had prior to any plan for detoxification. Starting medication such as clonidine or benzodiazepines prior to significant withdrawal symptoms can be extremely helpful. While these medications cannot fully alleviate withdrawal symptoms they can mitigate them to the point of comfort and decreased anxiety from the patient's standpoint. Again, utilization of methadone and buprenorphine in the setting of withdrawal and detox is an important discussion to be had early in the treatment pathway. If the patient will be placed on buprenorphine they should not be treated in the detox phase with methadone and vice versa.

There are three basic types of induction for patients with opioid use disorder. One would be to transfer the patient from one type of full agonist over to methadone, which is also full agonist. The second would be transfer from a fully detoxed opioid naïve patients to either a full agonist or a partial agonist. The third would be transfer from a full agonist over to a partial agonist such as buprenorphine. Induction of long-acting naltrexone or short-acting naltrexone should be done after the patient is completely withdrawn from all other opioids in the system. This can be done with an appropriate urine drug screen as well as appropriate education for the patient has to the risks and benefits of induction with this medication. They should be made aware that if any opioid or opioid like substances are in the system that the utilization of buprenorphine or naltrexone can cause rapid onset of precipitated withdrawal. If the patient is going to be placed on methadone while another agonist is in their system the patient should be made aware of the risks of early utilization of methadone and the risk of concomitant use of benzodiazepines in methadone induction. The patient should be told that these could lead to respiratory depression and accidental overdose. All methadone inductions should be done in a highly monitored fashion. This can be done in an outpatient setting with daily evaluation of the patient and visualize dosing. It is recommended that all induction on methadone be accomplished with specialty level

clinician observation. The induction onto buprenorphine following detoxification is relatively simple. Please refer to the buprenorphine section for a complete description. The induction of the patient onto buprenorphine while on a full agonist presents more challenges. This should be done under specialty level observation and with full array of risks, benefits and alternatives being given to the patient. Utilization of withdrawal adjunctive medication such as clonidine is highly recommended when switching from a full agonist to a partial agonist medication.

Maintenance dosing should be agreed upon by the patient, behavioral health staff as well as the clinician treating the patient. As a general rule the lowest dose that accomplishes the abatement of the opioid use disorder behaviors is the most appropriate maintenance dose. Higher doses cause more cognitive impairment as well as chronic adverse events such as constipation, memory deficits as well as tolerance and possible hyperalgesia when using methadone or buprenorphine. Therefore, if the patient can be adequately maintained on a buprenorphine dose such as 4 mg two times a day this would be preferred to 8 mg three times a day. However, appropriate craving abatement and ability to engage in meaningful behavioral health activities must be balanced with a lower dose. When utilizing medication such as naltrexone with the patient in early remission switching from the depot naltrexone to the oral naltrexone should be considered. These medications seem to have the same pharmacological efficacy and thus the effectiveness is only dependent on patient compliance. Therefore, a maintenance dose for naltrexone would preferably be given in the oral form.

Tapering of any of these medications is highly controversial. Information in the literature shows variable results with tapering, however, the most common outcome is a premature relapse.[28-30, 39] Given that long-term randomized control trials for tapering have only had negative results, tapering should be undertaken with extreme caution. If the patient is found to be in remission for greater than one year a “self-tapering” program may be initiated. Allowing the patient to help direct the tapering pathway is of

paramount importance, as they are the ones who are most likely to notice risk with the rapid taper versus slow taper. We would highly recommend against detoxing rather than tapering a patient off of these medications. Given that early cessation of these medications can lead to relapse it is recommended that these patients be able to obtain these medications in some cases for the remainder of their lifetime. However, over time with appropriate behavioral therapy and stabilization of social complications a large portion of patients may be able to taper off after 2 to 5 years of treatment. It is important to understand that forced tapering presents the highest risk for relapse and thus any attempt to force taper a patient is most likely to end in relapse of both utilization of the patient's drug of choice as well as a relapse in the behaviors associated with an opioid use disorder. This does not mean that patients should not be given encouragement and education about how to taper. It would be recommended that once a year the patient should be evaluated and educated on the possibility of tapering off of their medications. If this leads to a significant increase in opioid use disorder behaviors, significant anxiety or social impairment medication should be continued.

IX. General Behavioral Approach

Evidenced based therapy such as Cognitive Behavioral Therapy (CBT), contingency management or motivational enhancement therapy is an essential part of any comprehensive and successful opioid treatment program. Cognitive therapy or cognitive behavioral therapy as defined by its founder, Aaron Beck, "Is a form of psychotherapy in which the therapist and client work together as a team to identify and solve problems. Therapists use the Cognitive Model to help clients overcome their difficulties by changing their thinking, behavior, and emotional responses.".[40] Over 30 years of research has proven the effectiveness of CBT. Several studies have demonstrated neurobiological changes associated with CBT. [41]Its use in both individual and group settings is widely supported. CBT is effective for a variety of mental health as well as substance use disorder. "Evidence from numerous large scale trials and quantitative reviews supports the efficacy of CBT for alcohol and drug use disorders.[42] Providing the most effective treatment pathways for patients will yield long term recovery and an overall reduction in cost to the SUD treatment system.

Motivational interviewing (MI) and motivational enhanced techniques (MET) are also essential skills for opioid treatment program therapists. Motivational interviewing is a psychotherapy model developed for outpatient therapy and is an effective skill in concordance with cognitive behavioral therapy. Motivational interviewing was developed by Professors William Miller and Stephen Rollnick and is defined as "a method that works on facilitating and engaging intrinsic motivation within the client in order to change behavior. MI is a goal-oriented, client-centered counseling style for eliciting behavior change by helping clients to explore and resolve ambivalence."[43]

Motivational interviewing and motivational enhancement therapy techniques can be used as standalone interventions as well as in combination with cognitive behavioral therapy. As a standalone therapy, data

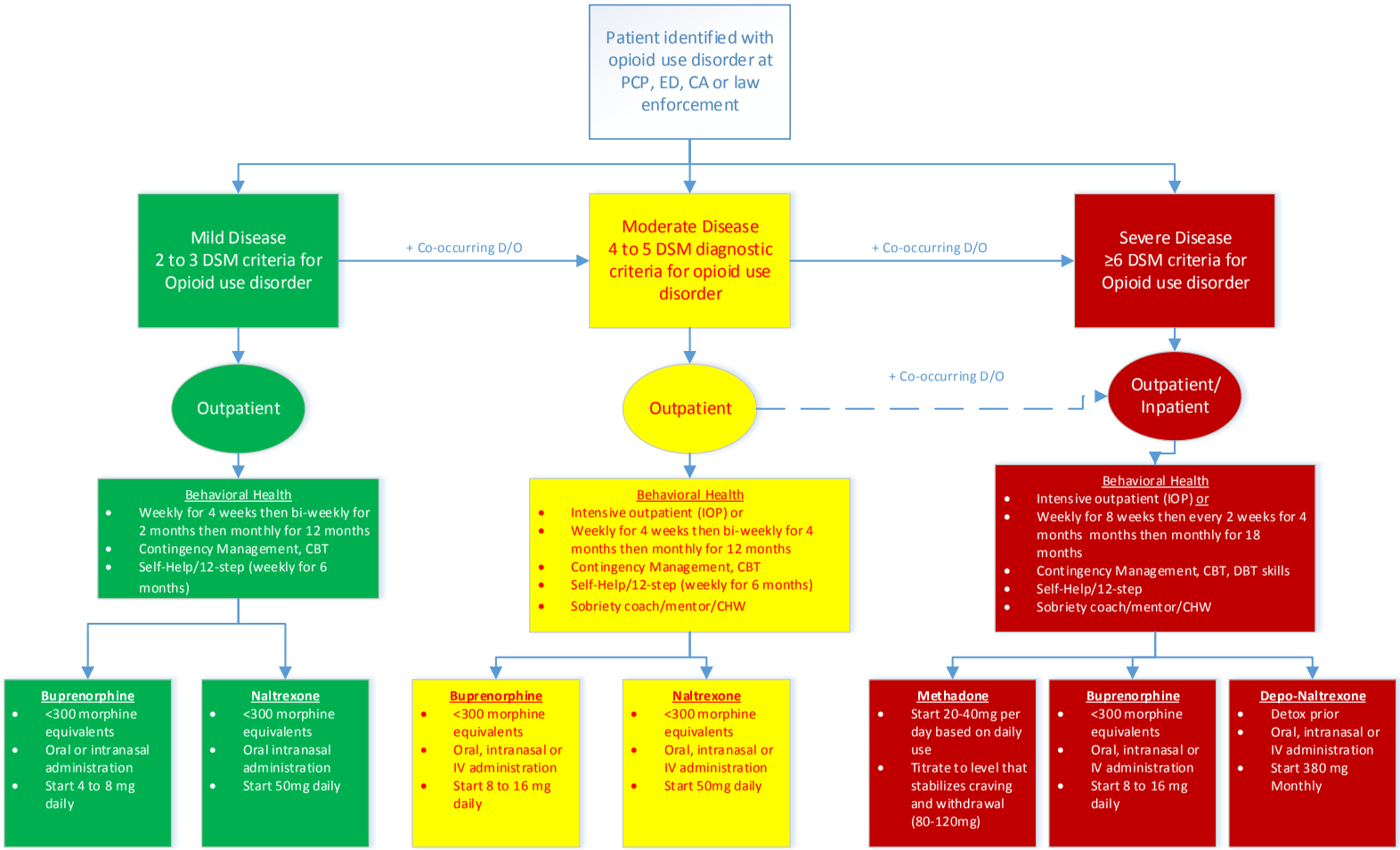
has shown its efficacy in the small to moderate range.[42] However, as a conjunctive therapy it can be highly effective, particularly in an individual therapy setting.

Contingency Management (CM) is perhaps the most underused evidenced based treatment for substance use disorders. There is a significant growing body of evidence proving this to be a highly efficacious treatment. Studies have shown this to be superior to relapse prevention and cognitive behavioral therapy in some cases.[44] "contingency management approaches are grounded in operant learning theory and involve the administration of a non-drug reinforcer (e.g. vouchers for goods) following demonstration of abstinence from substances." [42]research over the past 10 years or so has consistently shown its effectiveness in reducing substance use and related maladaptive behaviors.[44] Despite evidence to support its effectiveness, contingency management is not widely used. The intensity of cognitive and behavioral intervention that currently exists within the opioid treatment program structure is an excellent setting for incorporation of contingency management.

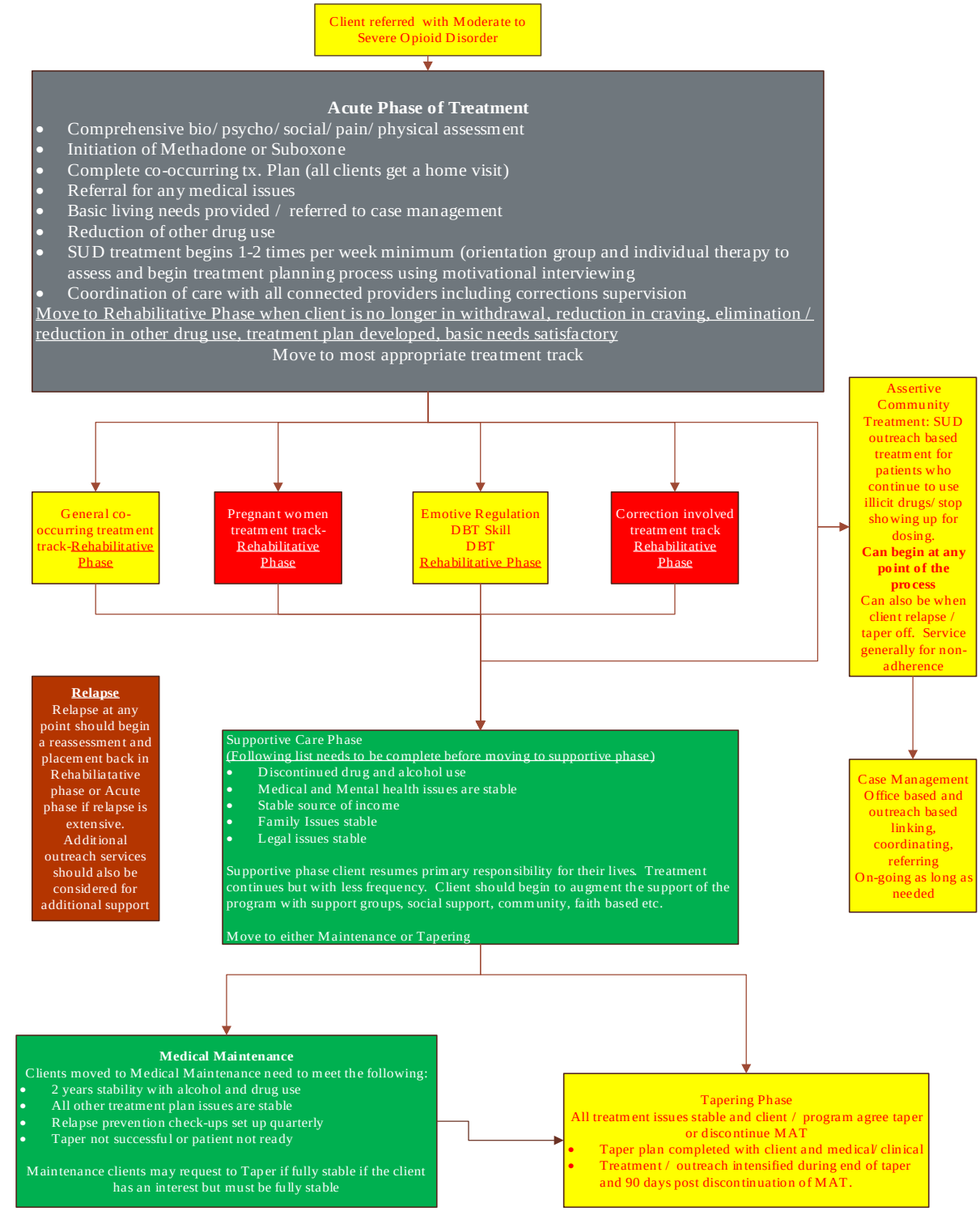
Incorporating evidenced based treatment practices into the opioid treatment programs is essential for positive functional outcomes. Therapists highly trained in cognitive behavioral therapy and motivational interviewing psychotherapy models in conjunction with contingency management are necessary pathways for patient long term success. This in turn leads to overall reduction in cost not only to the substance use disorder treatment system, but the public health and criminal justice systems as well.

Incorporation of 12 step self-help groups such as narcotics anonymous into the treatment pathway for patients who have opioid use disorders has had mixed results.[45-47] these mixed results may be due to the confounding variables of whether or not a given group "believes in" the utilization of opioid replacement therapy as an adjunct to treatment. If the group does not feel that this is the right thing to do then the patient is given advice that is in direct conflict with his or her treatment team advocating

the use of medication to help stabilize the neural axis and make behavioral therapy more effective. While the evidence is strong that this should not be the only pathway for a patient to obtain and maintain initial stabilization of an opioid use disorder it should be considered a viable adjunct as long as treatment pathways are well aligned. This may also help to reconstruct the patient's social sphere and allow them a safe place to talk about their disease. It is this author's opinion that utilization of a 12 step self-help group in conjunction with standard therapy such as cognitive behavioral therapy, contingency management or motivational enhancement therapy may provide increased stability in the long-term. Again, this is only if the treatment theories align.[45-47]


Patient identified with opioid use disorder at PCP, ED, CA or law enforcement
Mild Disease
2 to 3 DSM criteria for Opioid use disorder
+ Co-occurring D/O
Moderate Disease
4 to 5 DSM diagnostic criteria for opioid use disorder
+ Co-occurring D/O
Severe Disease
≥6 DSM criteria for Opioid use disorder
Outpatient
Outpatient
+ Co-occurring D/O
Outpatient/ Inpatient
Behavioral Health
Weekly for 4 weeks then bi-weekly for 2 months then monthly for 12 months
Contingency Management, CBT
Self-Help/12-step (weekly for 6 months)
Behavioral Health
Intensive outpatient (IOP) or
Weekly for 4 weeks then bi-weekly for 4 months then monthly for 12 months
Contingency Management, CBT
Self-Help/12-step (weekly for 6 months)
Sobriety coach/mentor/CHW
Behavioral Health
Intensive outpatient (IOP) or
Weekly for 8 weeks then every 2 weeks for 4 months months then monthly for 18 months
Contingency Management, CBT, DBT skills
Self-Help/12-step
Sobriety coach/mentor/CHW
Buprenorphine
<300 morphine equivalents
Oral or intranasal administration
Start 4 to 8 mg daily
Naltrexone
<300 morphine equivalents
Oral intranasal administration
Start 50mg daily
Buprenorphine
<300 morphine equivalents
Oral, intranasal or IV administration
Start 8 to 16 mg daily
Naltrexone
<300 morphine equivalents
Oral, intranasal or IV administration
Start 50mg daily
Methadone
Start 20-40mg per day based on daily use
Titrate to level that stabilizes craving and withdrawal (80-120mg)
Buprenorphine
<300 morphine equivalents
Oral, intranasal or IV administration
Start 8 to 16 mg daily
Depo-Naltrexone
Detox prior
Oral, intranasal or IV administration
Start 380 mg Monthly

Opiate Treatment Path Behavioral Health Paths For Moderate/ Severe Opioid Disease (No Client~~s~~ Administratively Discharged)



X. Medical Necessity

The general approach to a patient with an opioid use disorder, which has been agreed upon in the literature, includes utilization of medication, integrated behavioral health and help with stabilization of social issues. This includes availability of methadone, buprenorphine and naltrexone. This includes the availability of therapies such as cognitive behavioral therapy, motivational enhancement therapy, and contingency management made available in both the one-on-one and group delivery models. Social services in case management should be made available for those patients who require this. The vast majority of patients with a moderate to severe opioid use disorder will have issues with housing, transportation, socially stable systems of care as well as the ability to communicate on a regular basis. Given this, an outreach component with utilization of a sobriety coach/community health worker has been found to be helpful in bringing the treatment to the patient when the social issues become a significant barrier. It should also be understood that this disease occurs in many states. There is acute, maintenance, recovery and early remission phases of the disease and treatment followed by a long-term remission phase. All of these phases have a risk of relapse, however, the farther along the path that the patient goes the lower the risk of relapse.

The population further subdivides based on whether or not they have a co-occurring psychiatric illness, current pregnancy, involvement with the judicial system or significant co-occurring medical disease. Each of these subgroups requires a different set of treatment pathways during the acute, maintenance, recovery and remission phases. However the overriding concept is the availability of medication, behavioral health intervention and social management services. Some patients may not fit the above general treatment paradigm. These can include those patients who are about to be incarcerated who would not benefit from starting on medication assisted treatment, those patients who have significant

side effects or allergies to the medications that significantly impact their comorbid medical disease or those patients with a severe untreated psychiatric illness.

With a mild opioid use disorder the patient would meet 2 to 3 DSM V criteria met. If the patient does not have a co-occurring mental health disorder then they can be treated in the outpatient setting. The vast majority of behavioral health literature in substance use disorders shows that early high intensity intervention is more helpful than low intensity long-term intervention. Therefore, a system that allows for high intensity evaluation and treatment early with a tapering effect of behavioral health intervention is appropriate. Patients with mild disease and no co-occurring disorder should have therapy weekly for the first four weeks, then biweekly for the next two months of treatment and then monthly for the following 12 months (combined 15 months). This can include contingency management, cognitive behavioral therapy, dialectical behavioral therapy as well as many other forms of standardized behavioral therapy which can be given initially in the one-on-one treatment pathway and then followed in a group setting. Given that the overriding severity of illness is less, the highly structured methadone clinic environment and the high-intensity opioid methadone itself is not recommended. However, studies have shown that medication assisted treatment including the use of buprenorphine and naltrexone in oral form may be significantly helpful in stabilizing the patient's craving and behavior.[6,7,8]

If the patient is on less than 150 morphine equivalents of opioid and is using oral or intranasal delivery of this opioid then it would be appropriate to transition this patient onto 4 to 8 mg daily of buprenorphine. If the patient is on greater than 150 morphine equivalents then twice a day dosing may be more effective. If the patient meets the above criteria and once all urine drug screens are negative naltrexone can be started at 50 mg daily. This patient can be detoxed in the outpatient setting using adjunctive treatment such as clonidine, gabapentin or buprenorphine. Daily contact is recommended

during this outpatient detoxification phase as this is the higher risk time for a patient to relapse. However, the majority of current literature recommends that a mild form of this disease does not require inpatient and can be handled quite effectively in an outpatient setting.

The moderate form of the disease which meets 4 to 5 DSM diagnostic criteria for an opioid use disorder represents an increase in severity of illness. This category will also encompass those patients with a mild form of a substance use disorder but who also have a co-occurring mental health disorder. These patients again can generally be treated in the outpatient setting. They should also have medication assisted treatment and behavioral health treatment available with an increase in the intensity of both. These patients benefit from an early high-intensity behavioral health intervention with at least weekly visits for the first four weeks followed by biweekly visits for the next four months and then monthly visits for the next one year (combined 17 months). Again this may include, but not be limited to contingency management, cognitive behavioral therapy, dialectical behavioral therapy and motivational enhancement therapy. These behavioral therapies should initially be done in a one-on-one fashion with the behavioral health specialist and once the patient understands the basic behavioral health changes required, then a group setting may be utilized. I would also recommend weekly self-help groups including cognitive behavioral therapy or a 12-step-based methodology meeting at minimum weekly for the first six months. These patients should also have access to a sobriety coach/community health worker given that the increase in severity of the disorder usually correlates with an increase in the severity of social malevolence. Intensive outpatient management may also be utilized in this subset of patients in order to allow for a more highly structured environment. These patients may benefit from being seen in an opioid treatment program, however, in general it is still recommended that buprenorphine or naltrexone be utilized rather than methadone. If the patient and the treatment team decide on buprenorphine and the patient is on less than 300 morphine equivalents daily then the

patient can be transitioned to buprenorphine at the 8 to 24 mg per day with a split dosing schedule. This can then be titrated to the appropriate maintenance dose based on the patient's cessation of craving and addictive behaviors. This patient may also be started on naltrexone at 50 mg daily once they have been effectively detoxified from opioids.

Despite the innate desire to place these patients inpatient for opioid detox no studies show any difference in outcomes at one year if the patient is detoxified on and inpatient or outpatient basis. Therefore, if the patient does not have a co-occurring disorder along with moderate substance use disorder or has lack of housing or significantly dangerous living situation then detoxification can be done in the outpatient setting.

As a patient moves into the severe category of substance use disorder they are generally in the situation in which housing, transportation and outside support are unreliable at best. This may also be the same for patients with a moderate opioid use disorder and a co-occurring mental illness. Therefore, this subset of patients should be evaluated for inpatient detoxification and early stabilization. While the physiologic aspects of the disease can be treated in an outpatient detoxification fashion many of the social and psychological issues require higher intensity, which can be provided in man inpatient setting. As the disease severity increases so do the behavioral health ailments. Therefore, a patient in the severe or moderate category with a co-occurring mental health disorder should have a much more intense behavioral health approach. This can include, but is not be limited to, intensive outpatient management platforms or for office-based treatment pathways the behavioral health intervention should be at minimum weekly for eight weeks followed by biweekly for four months and then followed by monthly for 18 months (combined 24 months). This treatment should begin with basic dialectical behavioral therapy skills in association with contingency management and self-help/12-step group therapy. If the patient is not significantly opposed to this type of therapy it would be recommended that this patient

attends 12-step meetings daily for at least 30 days. This patient should also be assigned a sobriety coach/community health worker who would do an in-home assessment followed by outreach follow-up visits that include weekly interaction and frequency of visits that mirrors the behavioral health pathway.

Given the increased severity of illness, all medications should be available for utilization. This includes methadone, buprenorphine or depot naltrexone. If methadone is chosen the patient should be started on 20 to 40 mg per day in titrated to the level that stabilizes the patient. This is generally between 80 and 120 mg per day. If the patient started on buprenorphine after detoxification the patient should be started on 16 to 24 mg per day in divided doses. The patient may also be started on the standard 380 mg intramuscular depot naltrexone injection. The patient needs to be fully detoxified prior with a drug screen showing no opioids. Prior to initiation of depot naltrexone the patient must also demonstrate tolerance of an oral “test dose” prior to the administration of the long-acting injectable medication.

All of the above patients should have access to basic case management and office-based services as well as coordinating staff. This can be helpful in allowing the patient to stay up on all the paperwork required to maintain eligibility for public health insurance programs or any food or housing programs. Once the patients are “stable” and have been on a maintenance dose of medication for six months the patient can be referred to any specialty recovery programs such as those for patients with co-occurring disorders, patients who are pregnant or early postpartum as well as those involved in the correctional system. During this rehabilitative phase patient would be expected to have monthly urine drug screens at minimum, have discontinued or significantly decreased illicit drug use and/or alcohol use, have increased stability with their medical and mental health issues have identified a source of income as well as identified and are working toward resolution of any family issues or legal issues. Once this patient is been medically stable for 2 to 3 years it would be appropriate to evaluate the patient for possible

tapering.

When considering tapering one should understand that the literature is very clear that forced tapering or too rapid of a taper without patient involvement significantly increases the risk of relapse. Therefore, all tapering should be made in conjunction with behavioral health staff, the patient, and the treating physician. Allowing the patient to delineate their appropriate passive tapering and help direct the rate of tapering is imperative. Without this involvement, anxiety and the risk of relapse significantly increase. Approximately half of the patients for whom a taper is attempted will not be able to complete the taper. While it is appropriate to revisit the possibility of tapering at least yearly after a patient has been stable for two years there are some patients who may require a lifetime of treatment, as this is a chronic neurobiological disease and in many patients creates a permanent injury to the brain requiring long-term medication management. While we find in extinguishing effect from behavioral health interventions we do not find an extinguishing effect with medication. Therefore, it is recommended that no limits be placed on length of use of these medications as long as the patients are evaluated annually after the first two years for the possibility of tapering. If the patient continues to meet criteria for moderate or severe disease a taper should not even be considered. If the patient is not successful on this medication regimen despite maximal behavioral and social intervention then one of the other medications should be considered for use. This should be presented as a failure of therapy and not a failure of the patient. An example of this would be a patient who has been on buprenorphine at 8 mg three times a day for six months who has had multiple positive urine drug screens and consistently shows behaviors that keep them at the moderate to severe opioid use disorder. While this patient may not be successful on buprenorphine, a transition to methadone or naltrexone may significantly improve this patient's behavior by decreasing craving and changing the neural axis that is affected.

It is significantly important that all patients are screened and aggressively treated for co-occurring mental health disorders. This includes evaluation for any thought disorders, depression, anxiety as well as any disorders associated with inappropriate social interaction. If the addiction specialist physician is not capable of doing a full psychiatric evaluation on patients then they should be referred to an appropriate specialist who has the capability to diagnose and treat these disorders. Many studies have shown that without concurrent treatment of the co-occurring mental health disorder stabilization of the substance use disorder is unlikely. This includes the appropriate utilization of medication directed specifically toward the mental illness. It should also be understood that even if the mental illness is appropriately treated, this will not eliminate the existence of a substance use disorder. Therefore treating both concurrently is essential.

XI. Methadone

Methadone is a synthetic opioid analgesic that is used as an alternate to morphine and hydromorphone for patients with severe pain and remains the most studied and most accepted treatment for heroin addiction. Methadone has an asymmetric carbon atom resulting in 2 enantiomeric forms, the d and l isomers. The racemic mixture (dl-methadone) is the form commonly used clinically. Levo-methadone is a full μ-opioid agonist. Dextro-methadone does not affect opioid receptor but binds to the glutamatergic NMDA (N-methyl-D-aspartate) receptor, and thus acts as a receptor antagonist against glutamate. Methadone has been shown to reduce neuropathic pain in rat models, primarily through NDMA antagonism. Glutamate is the primary excitatory neurotransmitter in the CNS. Acting as an NMDA antagonist may be one mechanism by which methadone decreases craving for opioids and tolerance, and has been proposed as a possible mechanism for its distinguished efficacy regarding the treatment of neuropathic pain. The dextrorotary form (d-methadone) acts as an NMDA antagonist and is devoid of opioid activity: it has been shown to produce analgesia in experimental models of chronic pain.

Methadone has a slow metabolism and very high fat solubility, making it longer lasting than morphine-based drugs. Methadone has a typical elimination half-life of 15 to 60 hours with a mean of around 22. However, metabolism rates vary greatly between individuals, up to a factor of 100,[48] ranging from as few as 4 hours to as many as 190 hours.[49] This variability is likely due to genetic variability in the production of the associated enzymes that metabolize methadone are CYP3A4, CYP2B6 and CYP2D6. Many substances can also induce, inhibit or compete with these enzymes further impacting (sometimes dangerously) methadone half-life. A longer half-life frequently allows for administration only once a day in opioid detoxification and maintenance programs. Patients who metabolize methadone rapidly, on the other hand, may require twice daily dosing to obtain sufficient symptom alleviation while avoiding excessive peaks and troughs in their blood concentrations.[49] This can also allow lower total doses in

some patients. The analgesic activity is shorter than the pharmacological half-life; dosing for pain control usually requires multiple doses per day.

As with other opioid medications, tolerance and dependence usually develop with repeated doses. Tolerance is the body's physical adaptation to an ever increasing dose of the medication which leads to a decrease in effectiveness of that medication. Dependence is a portion of physical adaptation that would have a withdrawal syndrome if the medication was abruptly stopped. There is some clinical evidence that tolerance to analgesia is less with methadone compared to other opioids; this may be due to its activity at the NMDA receptor. Tolerance to the different physiological effects of methadone varies; tolerance to analgesic properties may or may not develop quickly, but tolerance to euphoria usually develops rapidly, whereas tolerance to constipation, sedation, and respiratory depression develops slowly if at all.

Methadone Safety

Respiratory depression, including fatal cases, have been reported during initiation and conversion of patients to methadone, and even when the drug has been used as recommended and not misused or abused. Proper dosing and titration are essential and tablets should only be prescribed by healthcare professionals who are knowledgeable in the use of methadone for detoxification and maintenance treatment of opioid addiction. It is essential to monitor for respiratory depression, especially following a dose increase. The peak respiratory depressant effect of methadone occurs later, and persists longer than the peak pharmacologic effect, especially during the initial dosing period. An effective means of risk mitigation is the prescribing of an opioid reversal kit containing naloxone.

QT interval prolongation and serious arrhythmia (torsades de pointes) have occurred during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for

maintenance treatment of opioid addiction. Clinicians must monitor patients for changes in cardiac rhythm during initiation and titration of methadone. The true risk of chronic QT prolongation is still under intense investigation and given the large numbers of people on methadone and the fact that – due to cardiac arrhythmia is no higher in a methadone clinic versus the public, one would suspect this may be over stated.

The use of methadone in patients who are pregnant has been shown to be safe. While it is a pregnancy category C medication and increases the risk for neonatal abstinence syndrome these are known and treatable issues. The benefits of stable opioid dosing and helping patients to avoid use of other drugs of abuse significantly outweigh the risks of methadone utilization. The significant risk to the pregnant patient is preterm labor secondary to acute withdrawal from opioids. Therefore, this medication should not be stopped and if at all possible use of opioid antagonists should be avoided. Thus far there is no significant study that shows it is unsafe for breast-feeding. Therefore, we would recommend continuation of breast-feeding while the mother is being treated with methadone. Breast-feeding has also decreased the need for the newborn's stay in the neonatal ICU. The amount of methadone in the breast milk is highly variable however the American Academy of Pediatrics recommends continuation of breast-feeding no matter the dose of methadone by the mother.

Assessing a Patient for Opioid Treatment Program Initiation

There are a number of important areas to concentrate on with regards to patient history for this population of patients.

1. Ensure the patient meets the DSM 5 criteria for moderate to severe opioid use disorder.
2. Identify any potential risks for methadone toxicity prior to opioid treatment program initiation
3. Pattern of use of all major drug classes (including tobacco and alcohol).
4. Previous addiction treatment history and response.
5. High risk behavior such as needle sharing and exchanging sex for drugs.
6. Psychiatric history and current mental status including suicidal ideation.
7. Social situation including housing, supports, child custody, and partner's drug-use history.
8. Details regarding chronic or recurrent pain.

Patient Factors that Increase Risk of Methadone Toxicity

1. Recent benzodiazepine use
2. Use of other sedating drugs
3. Alcohol-dependent patients
4. Over 60 years old
5. Respiratory Illnesses
6. Taking drugs that inhibit methadone metabolism
7. Lower opioid tolerance
8. Liver disease
9. Recent discharge from inpatient rehabilitation facility
10. Recent incarceration

Elderly

One study showed that older adult OTP patients (> 55 years old) were more likely to report alcohol use, and in general, their quality of life did not improve with aging and length of tenure in OTP.[50] Firoz and Carlson did not find any differences between opioid treatment program patients older than 55 years and their younger counterparts in terms of medical, psychiatric or employment problems[51]. Schroeder et al provided strong evidence of the significantly higher rates of adverse events (infections, gastrointestinal, musculoskeletal) among female opioid treatment program patients, while participants over age 40 reported lower rates of adverse events.[52] Tuchman reported that close correspondence of menopausal symptoms and opiate withdrawal/methadone symptoms can result in inadequate medical attention to problems related to methadone maintenance [53-55].

Focused Physical Examination

The opioid treatment program physician should conduct a comprehensive physical examination prior to initiating treatment. Special attention should be given to signs of opioid withdrawal, malnutrition, jaundice, hepatosplenomegaly, cardiovascular and respiratory status, pupil size, needle tracks, and abscesses.

Initial urine drug screening and utilization of the prescription drug monitoring program (PDMP/MAPS) facilitates objective corroboration of the patient history of opioid drug use. Some particular urine drug screen results need to be taken into consideration prior to opioid treatment program initiation. On October 26, 2013 the American Society of Addiction Medicine released a white paper concerning drug testing. Please refer to this white paper for specifics regarding frequency and type of drug testing to be done.

A patient may be appropriate for initiation on methadone even if their initial urine drug screen is positive for opioids, but does not identify the specific opioid that the patient has reported as their opioid of abuse, if the following circumstances are met:

1. The patient has signs and symptoms of obvious opioid withdrawal
2. The patient has obvious track marks
3. The patient has previously been on methadone
4. The physician has corroborating information from a previous opioid prescribing physician.

There are many patients who come for an initial assessment for opioid treatment program who have previously tried/used methadone that was not prescribed for them. With a positive initial urine drug screen for methadone or EDDP (a methadone metabolite), it is important to document the patient's history of methadone use.

Patients are at a high risk of death from methadone overdose in the first two weeks of Methadone induction. Recent prospective population studies from the UK and Australia have revealed that during the first two weeks of methadone treatment the crude mortality rate was 17 per 1000 person years. [56, 57] The risk of fatal methadone overdose during this time period is estimated to be 6.7 times higher than that of heroin addicts not in treatment, and 98 times higher than that of patients on maintenance doses of methadone in treatment for longer periods. [58] A single day's methadone dose can be lethal

to non-tolerant individuals. The ratio between the maximum recommended initial dose (30 mg) and a potentially fatal single dose is exceedingly narrow compared to other medications.

The prolonged half-life (as long as 55 hours in methadone naïve individuals) and the large volume of distribution of methadone accounts for the insidious onset of overdose. During dose increases, serum levels accumulate over several days even if the dose is kept the same. Therefore, a dose that is barely adequate on the first day can be toxic by day 3-5. This is particularly relevant during initiation on methadone. The patient may appear relatively alert during the day succumbing to an overdose during a nap or at night. Early signs of toxicity include ataxia, slurred speech, "nodding off," and emotional liability. [58]

Concurrent use of benzodiazepines, alcohol, and other sedating drugs substantially increases the risk of death from methadone toxicity. One study found evidence of polydrug use in 92% of methadone-related deaths. [59] Animal studies indicate that benzodiazepine use substantially increases the risk of fatal overdose.

Reducing Overdose Risk

1. Explain to the patient that it takes several weeks to reach the optimal dose of methadone, and it may be dangerous to try to relieve withdrawal symptoms with benzodiazepines, illicit methadone or other drugs.
2. Advise the patient to limit his or her driving or use of machinery after a dose increase, particularly in the first few hours after dosing. Take the methadone dose in the morning, since the risk of overdose is increased at night.
3. Whenever feasible (with the patient's consent), a family member or significant other should be educated about the symptoms of overdose with clear instructions to seek urgent medical help at the first sign of toxicity. A patient information guide may be used for this purpose.

4. Schedule patient visits at least every 1-2 weeks. However, twice-weekly visits during the first two weeks of treatment are recommended, particularly if the patient is at increased risk for methadone toxicity. The physician can schedule an assessment of the patient two to six hours after the methadone dose if there are concerns about sedation with the dose. The physician should inquire about sedation and other side effects.
5. Careful monitoring of take-home doses is needed during the first month of treatment including Sunday take-home doses, holiday carries, pharmacy closure.
6. Avoid initiating sedating drugs and warn the patient to avoid using them. This includes alcohol, benzodiazepines, sedative-hypnotics, antipsychotics, antidepressants, and sedating antihistamines. Even moderate, therapeutic doses of these drugs may increase the risk of overdose if they are initiated at the same time as methadone and the patient is not fully tolerant to their sedating effects. Patients should also be advised to avoid alcohol during OTP initiation.
7. Benzodiazepine use disorders are common in this population. As with opioids, it is difficult to accurately judge a patient's benzodiazepine use and tolerance, therefore, benzodiazepine tapering, while difficult on its own, can be very complicated and potentially unsafe (due to over sedation) when attempted with methadone initiation. If possible, patients taking high doses (50 mg of diazepam equivalent per day) should be tapered prior to methadone initiation. Otherwise, benzodiazepine tapering, during initiation should be considered, with monitoring in a medically supervised setting. Abrupt cessation of high doses of short-acting benzodiazepines can precipitate acute withdrawal and delirium tremens, which is fatal in up to one third of cases if left untreated. Only small benzodiazepine doses should be used, just enough to prevent severe withdrawal. Consultation with an addiction psychiatrist is advised if available.

8. At any stage of methadone based treatment, the dosing nurse should be instructed to hold the methadone and alert the physician if the patient appears sedated or intoxicated.
9. Careful assessment prior to dose increases.

Induction

The physician should base the initial dose on the patient's underlying risk for methadone toxicity.[60] Sedating drugs include over-the-counter medication such as Benadryl, prescribed medications such as antipsychotics and sedating antidepressants, or drugs of abuse such as ketamine, GHB and medical grade marijuana. Even therapeutic doses of benzodiazepines can increase risk of methadone toxicity. The opioid treatment program physician should look for evidence of benzodiazepine use in the initial drug screen. Opioid tolerance is difficult to establish by history, so, if in doubt, it is safer to initiate on a lower dose. Lowered tolerance is likely in patients who report non-daily opioid use, daily use of codeine, or daily use of oral opioids at moderate doses. Typically, patients who use opioids intranasally (ie snorting) have a lower tolerance than patients who inject opioids. Tolerance is lower in patients who have been abstinent for more than a few days, e.g., patients who have been recently discharged from a correctional facility, detox center or treatment center. Also those patients who had recently been on long-acting naltrexone will show a much lower tolerance.

Patient Factors Initial Dose

1. Higher risk for methadone toxicity 20 mg or less
2. Recent abstinence from opioids 10 mg or less
3. No risk factors or recent abstinence 30 mg or less

Early Stabilization Phase (0-2 weeks)

Dose increases during the early stabilization phase should take place only after an in-person opioid treatment program physician assessment and for patients who are experiencing cravings, ongoing

opioid use, and/or a cluster of opioid withdrawals symptoms. Opioid treatment program physicians should assess patients at least once weekly during this phase.

Dosing During Early and Late Stabilization Phase

1. Patient Factors Dose Increase Frequency
2. Higher risk for methadone toxicity 5-10 mg Every 3-5 days
3. Recent abstinence from opioids 5 mg or less Every 5 days or more
4. No risk factors or recent abstinence 10-15 mg Every 3-5 days

Missed Doses During Early Stabilization Phase (0-2 weeks)

During the early stabilization phase, patients should be on the same dose for at least 3 consecutive days with no missed doses before an increase. The dosing nurse should be advised to contact the opioid treatment program clinician if the patient misses any doses. If two consecutive doses are missed during the early stabilization phase, the dosing nurse should be advised to cancel the prescription until the patient can be reassessed by the physician. Collaborative communication between the clinician and dosing nurse if the patient misses any doses during early stabilization is essential. The patient must be reassessed in person by the physician and restarted at 30 mg or less.

Late Stabilization Phase (2-6 Weeks)

Most patients in the late stabilization phase are taking between 50–80 mg of methadone. Most patients during this phase are experiencing only partial relief of withdrawal symptoms, and they often continue to use opioids intermittently. Dose increases during the late stabilization phase shall be the same as during early stabilization phase until a dose of 80 mg is reached. Dose increases during the late stabilization phase should take place with an in-person opioid treatment program clinician assessment and for patients who are experiencing cravings, ongoing opioid use, and/or a cluster of opioid withdrawal symptoms. Opioid treatment program clinicians should assess patients at least once weekly during this phase.

Missed Doses During Late Stabilization Phase

If three or more consecutive doses are missed during the late stabilization phase, the pharmacist should be advised to cancel the prescription until the patient can be reassessed by the OTP physician. The patient must be reassessed in person by the OTP physician. After 3 consecutive days missed, the dose should be decreased to 50% of the current dose or 30mg. After 4 or more consecutive days missed, the dose should be decreased to 30 mg or less.

Maintenance Phase (6+ Weeks): The Optimal Methadone Dose

The optimal maintenance dose of methadone will relieve withdrawal symptoms, partially block opioid induced euphoria and reduce opioid cravings for 24 hours, without causing sedation or other significant side effects. With experience, the opioid treatment program clinician can reach this dose for the majority of their patients within 2-8 weeks of initiating methadone. The optimal dose range for most opioid treatment program patients is 60-120 mg.[61-63] A meta-analysis by Bao et al reported that doses of methadone between 60-120 mg and individualization of doses are associated with better retention in opioid treatment program. During the maintenance phase (when the dose is 80 mg or more) the OTP physician shall increase the dose by no more than 5-10 mg every 5-7 days. Dose increases during the maintenance phase should take place with an in person opioid treatment program clinician assessment and for patients who are experiencing cravings, ongoing opioid use, and/or a cluster of opioid withdrawal symptoms. Opioid treatment program clinicians should assess patients once weekly when ongoing dose adjustments are occurring and less frequently thereafter if required.

Missed Doses During Maintenance Phase

Standards for missed doses during maintenance are the same as those for late stabilization.

Doses Below 60 mg

There is evidence that methadone doses of 60–100 mg are more effective than doses below 60 mg in reducing heroin use and retaining patients in treatment.[64] However, maintenance doses below 60 mg

are justified for patients who have no unauthorized opioid use, report no significant withdrawal symptoms or cravings, are at high-risk for methadone toxicity, or are on a tapering protocol.

Doses Above 120 mg

Opioids such as methadone have several side effects that may be dose related, including sedation, overdose leading to death, sleep apnea and sexual dysfunction. High methadone doses are also associated with prolonged QT interval, which can cause Torsades de Pointes, a ventricular arrhythmia.[65] One study found that approximately 5% of patients on methadone maintenance had QTc > 500 msec, the value associated with increased mortality. All of these patients were on doses in excess of 120 mg. [66] Other risk factors for Torsades include, use of cocaine and other stimulants, heavy alcohol consumption, cardiomyopathy, previous MI or valvular abnormalities, a family history of long QT syndrome, liver dysfunction, electrolyte disturbances and medications that affect methadone levels or the QT interval.[65] However, there is still significant debate about the relevance of prolonged QT syndrome in a chronic setting rather than the acute formation of its prolonged QT. There is not enough evidence to state that every patient on methadone maintenance therapy should receive a 12 lead EKG.

Assessment and Monitoring

High doses of methadone can sometimes have sedating effects that may not be apparent in the physician's office. The OTP physician should inquire about whether the patient or the patient's family has observed cognitive effects such as "nodding off", lethargy, diminished concentration or memory. At baseline, the physician should identify risk factors for torsades, such as heart disease, family history of sudden cardiac death, or concurrent use of medications that affect QT interval. An ECG shall be done on patients whose dose is greater than 150 mg [67] and repeated for doses of 180-200 mg. Patients with known risk factors for Torsades should have an ECG at a dose above 120 mg.

Management of High Doses

A trial of tapering is indicated for patients who report sedation when on high doses. Clinical experience suggests that tapering to an overall dose decrease of 20-40 mg is tolerated well, and patients often report that they feel more alert and energetic. Cardiology referral and/or methadone dose reduction should be considered when the QTc exceeds 500 msec, and the opioid treatment clinician should take steps to modify risk factors when possible.

Ongoing Withdrawal Symptoms in Patients on High Doses

Patients with ongoing withdrawal symptoms despite high methadone doses require ongoing assessment by the OTP physician. Possible causes include, rapid metabolism of methadone. Although controversial, peak and trough levels might be useful in patients who continue to report withdrawal symptoms despite doses of 120 mg or higher.

Use of medications that increase the metabolism of methadone such as phenytoin, chronic alcohol use may increase risk. Continued opioid use causes increased tolerance and withdrawal symptoms on opioid cessation. Dose diversion where the patient consumes some of his/her take-home dose and sells the rest.

“Pseudonormalization” can occur after a methadone dose increase, some patients experience very mild mood elevation. They develop tolerance to this effect after a few weeks, prompting them to seek another dose increase. Insomnia, anxiety, fatigue and other psychiatric symptoms are such a prominent feature of opioid withdrawal, patients may incorrectly attribute these symptoms to withdrawal. Since cocaine is a methadone inducer (increases the metabolism of methadone), especially when used in large doses, ongoing use of cocaine may result in the patient complaining of the need for a dose increase.

Managing Missed Doses

Missed doses may indicate a variety of problems, including relapse to alcohol or other drug use. Therefore, the physician should reassess the patient’s clinical stability. Dosing personnel should report missed doses to the OTP physician in a timely fashion. A clinically significant loss of tolerance to opioids

may occur within as little as 3 days without methadone; therefore the opioid treatment clinician should reduce the methadone dose in patients who have missed three consecutive days. The dose can be rapidly increased once the response to the lower dose is assessed.

Phase of Treatment	Missed Doses	Action	Dose Change
Early Stabilization	24 hours missed	No dose increase	resume same dose
	48 hours	Reevaluate patient	Start from initial dose
Late Stabilization/ Maintenance	1-2 days	If patient not intoxicated continue current dose. Urine drug screen.	No change
Late Stabilization/ Maintenance	3 days	Reassess Patient Urine Drug Screen	Restart at 50% of dose, then increase dose to no more than 10 mg daily for a maximum of 3 days
Late Stabilization/ Maintenance	4 or more days	Reassess Patient Urine Drug Screen	Restart at 30 mg or less and titrate per usual

Vomited Doses

Vomited methadone doses are not replaced unless a health professional or staff member directly observes emesis. If the emesis was witnessed by the dosing nurse or staff, and it occurred less than 15 minutes after consumption, the dose can be replaced at no more than 50% of the regular dose. Repeated dosing (i.e. replacement) creates a risk of inadvertent overdose. Underlying causes of the vomiting should be addressed. For pregnant patients or patients with underlying medical conditions (eg cancer or HIV), the opioid treatment clinician may decide to prescribe a replacement dose even if the pharmacy or clinic staff did not observe emesis.

Take Home Doses

Take-home dose policy should mirror that developed by the state in which the methadone is being prescribed. Patient should have a significant improvements and level of disease and they should meet at maximum a mild opioid use disorder while on therapy. However, it is recommended that the patient be listed as in remission from the behaviors of active addiction. After initial take-home doses are started the patient should be evaluated for presence of methadone in their urine, as well as presence of other illicit drugs with particular attention to benzodiazepines.

Take-home medication, or “carries” is a therapeutic tool to assist patients in re-establishing their lives constructively. Carries can also help the patient to avoid other persons who may trigger further illicit drug use. However carries also incur a risk of diversion, the main problem being the danger to others from respiratory depression which can be fatal, especially to children, and those adults not tolerant to methadone. The decision to allow carries is not a time-based decision.

1. Carry or take-home medication is not recommended during the first three months of treatment. There must be a rationale for granting carries. For instance unemployed patients would not usually require carries.
2. Physician's records must justify the decision to grant carries.
3. Carry or take-home medication may be given to patients who are considered to be functionally stable. A decision to grant carries should ideally be made in consultation with other professionals involved, such as counsellors and dosing nurses.
4. A patient who is still using any other drug of abuse, prescribed or not, should not be granted take home doses.

Stability may be assessed by a measured consideration of behavioral and other criteria, including the following:

1. Program participation:
    a. attends as required for methadone
    b. attends scheduled appointments
    c. complies with treatment agreement
2. Cognitive stability including the ability to assume responsibility for the care of the medication and to use it as prescribed.
3. Improvement in drug use (as evidenced by acceptable urines for 3 months), either abstinence or non-harmful use of drugs (harm can be seen as a continuum and can result from a single use or from long term use of drugs).
4. Confirm social integration, including:
    a. Full time employment
    b. Full time school attendance
    c. Full time child care responsibilities
    d. Full time volunteer work.
5. Patients who continue to use non prescribed mood-altering drugs are not candidates for carry privileges. Continuing drug use indicates patient's instability.
6. Patients who are eligible for and receive carry medication must accept the responsibility for the take-home methadone doses and use them for their intended purposes.

Some diversion of methadone certainly occurs. Patients who have take-home medication should be informed that they may be asked at any time to appear in the clinic and bring with them the remainder of their carry medication. Those who cannot bring in all their remaining sealed carries should be suspected of diversion; carry privileges may then warrant revision. Carry privileges must be stopped by the prescribing physician if he/she believes that the safety of the patient or that of others is at risk. Situations where the modification of carry medication must be considered include:

1. Reasonable evidence that the patient has failed to meet the terms of the treatment agreement.
2. Use of unauthorized drugs.
3. the patient has produced an unacceptable urine sample or has tampered with the collection of his/her required urine sample (for example, but not limited to, substituting another person's urine or some other material for his/her own urine; adding some contaminant to the urine sample submitted; providing a previously collected (i.e. "stale") sample of his/her own urine instead of a fresh sample collected under supervision; diluting his/her own urine sample).
4. Credible evidence that the patient has approached another methadone-treated patient suggesting or proposing to sell, buy, or share any urine sample, or to tamper with any urine sample.
5. Credible evidence that the patient has diverted, or allowed to be diverted, any part of his/her methadone (i.e. has failed to consume all or part of the methadone dose prescribed for him/her and allowed it to become available for use by anyone else)
6. Credible evidence that the patient has approached another person suggesting or proposing to sell, buy, or share methadone

A lock box is mandatory to store medication at home. It is the responsibility of the prescribing physician to make the final decision whether to approve a request for carries.

Withdrawal from Methadone Maintenance Treatment

In general there are only three reasons for withdrawal from methadone maintenance treatment. The first would be, the patient who has been stable for 2 to 3 years and is attempting to taper down so that they may become drug-free. The second would be a failure of methadone as the drug of choice for medication assisted treatment. And the third would be significant and persistent aberrant behavior that has been refractory to correction. Removing a patient from methadone maintenance treatment without a plan for continued care will lead to early relapse with an increase in mortality rate for this population.

If the above issues have arisen then patient should be set forward with one of two general pathways. The first would be a more rapid taper which could be for patients who will become incarcerated or otherwise need to be in a drug-free environment. This can be done by a 10% per day decrease in the dose of methadone, the utilization of clonidine as well as gabapentin or benzodiazepines can be necessary. The second is a more prolonged and controlled weaning which would be a 5% per day weaning of dose. This may also include utilization of clonidine, but should not require other adjunctive medication such as gabapentin or benzodiazepines. The immediate cessation of methadone except in the most extenuating circumstances should be considered unethical.

XII. Buprenorphine

Buprenorphine is a semi-synthetic opioid that is used to treat opioid addiction in higher dosages (>2 mg), to control moderate acute pain in non-opioid-tolerant individuals in lower dosages (~200 μg), and to control moderate chronic pain in dosages ranging from 20–70 μg/hour. It is available in a variety of formulations: Subutex (buprenorphine), Suboxone (buprenorphine and naloxone), Zubsolv (buprenorphine HCl and naloxone HCl), BUNAVAIL™ (buprenorphine and naloxone) Buccal Film, Buprenex (solutions for injection often used for acute pain), and Butrans (transdermal preparations used for chronic pain).

Buprenorphine hydrochloride was first marketed in the 1980s by Reckitt & Colman (now Reckitt Benckiser) as an analgesic, generally available as Temgesic 0.2 mg sublingual tablets, and as Buprenex in a 0.3 mg/mL injectable formulation. In October 2002, the Food and Drug Administration (FDA) of the United States also approved Suboxone and Subutex, buprenorphine's high-dose sublingual tablet preparations indicated for detoxification and long-term replacement therapy in opioid dependency, and the drug is now used predominantly for this purpose. Similar to methadone it can be written for pain off-label without requiring a special DEA license.

Buprenorphine is a semi-synthetic derivative of thebaine, one of the most chemically reactive opium alkaloids. Buprenorphine is a μ-opioid receptor agonist with high affinity, but low intrinsic activity. Compared with morphine, buprenorphine is considered a partial μ-opioid agonist displaying high affinity for and slow dissociation from the μ-opioid receptor. A full dose-dependent effect on analgesia has been seen within the clinically relevant dose range (up to 60 mg), with no respiratory depression. [68, 69] Clinically, there is also a less marked effect of buprenorphine-binding to μ-opioid receptors on gastrointestinal transit times, and indeed constipation seen in the clinic is remarkably low. [70] Buprenorphine also shows partial agonistic activity at the opioid receptor-like receptor 1 (ORL1)-

receptors which are (at least at supra-spinal receptors) postulated to induce a pronociceptive effect. ORL1-activation also has an effect on hyperalgesia. It might be that buprenorphine's partial agonism reduces this effect compared with full ORL1-agonists such as morphine or fentanyl. Buprenorphine's antagonistic action at the δ-receptors which have a marked anti-opioid action and seem to negatively modulate central analgesia seems further to contribute to its clinically seen analgesic effect. Its likewise antagonistic activity at the κ-opioid receptors might explain the fact that it induces much less sedation and psychotomimetic effects than morphine or fentanyl.[71] Animal studies have shown that buprenorphine has a 20–40 times higher potency than morphine.

The strong binding of buprenorphine to the μ-opioid receptor has several consequences. Initial binding is relatively slow compared with other opioids such as fentanyl.[72] However, the onset of analgesia is not dissimilar, since buprenorphine achieves effective analgesia at relatively low receptor occupancy (5%–10%) and thus relatively low plasma concentrations of buprenorphine are sufficient to provide effective pain relief. The slow dissociation of buprenorphine from the receptor results in a long duration of effect and also confers another advantage in that when the drug is withdrawn an abstinence syndrome is rarely seen because of the long time taken for the drug to come off the receptor.[73, 74]

The principal drug interactions of buprenorphine relate to its opioid activity. Buprenorphine exerts additive CNS and respiratory depressant effects when used in conjunction with other sedating medications. These include benzodiazepines, alcohol, tricyclic antidepressants, and sedating antihistamines. Deaths have been reported involving the combination of buprenorphine with high doses of benzodiazepines. Buprenorphine has a higher affinity for mu opioid receptors than the opioid antagonists. In the event of overdose of buprenorphine high doses of naloxone (10mg or more) may be required to reverse its effects. Naltrexone can precipitate a delayed withdrawal reaction in patients on buprenorphine. Buprenorphine exerts a degree of blockade to the effects of full agonist opioids which may complicate the use of additional opioids for analgesia. The initial dose of buprenorphine can

precipitate opioid withdrawal in patients with high levels of physical dependence to full opioid agonists. Buprenorphine is metabolized by the hepatic microsomal enzyme system (CYP 3A4). Theoretically, the use of foods or medications that inhibit the 3A4 enzyme (such as fluconazole, metronidazole, indinavir, ritonavir, erythromycin) may lead to increased plasma levels of buprenorphine whereas exposure to substances that induce the 3A4 system (such as phenobarbital, rifampin, phenytoin, carbamazepine, nevirapine) may lead to decreased levels of buprenorphine. Clinically, these medications have relatively minimal impact on buprenorphine dosing requirements. Each patient should be managed on an individual basis.

BUPRENORPHINE SAFETY

Buprenorphine has a favorable safety profile. Because of the “ceiling effect” of mu opioid receptor activation, respiratory and central nervous system depression is significantly less with buprenorphine as compared to full opioid agonists. In adults, overdoses on buprenorphine alone are almost never (if ever) fatal. However, it is possible for non-tolerant individuals to overdose on buprenorphine. Therefore, care should be taken in prescribing buprenorphine to individuals who are not fully tolerant to opioids. Fatalities have occurred primarily when buprenorphine was used intravenously along with intravenous benzodiazepines. It is important for a physician to be aware of the patient‘s concomitant use of other sedative hypnotics such as benzodiazepines. If the use of benzodiazepines or other CNS depressants is deemed medically appropriate, it is important to monitor closely for side effects, particularly sedation and respiratory depression.[75]

The use of buprenorphine in patients who are pregnant has been shown to be safe. While it is category C and increases the risk for neonatal abstinence syndrome these are known predictable, manageable problems. It has however been recently shown to have less risk of neonatal abstinence syndrome than methadone. [76, 77] The benefits of stable dosing and a patient not currently using other drugs of abuse significantly outweigh the risks of buprenorphine utilization. The significant risk to the pregnant patient

is preterm labor secondary to acute withdrawal from opioids. Therefore, this medication should not be stopped and if at all possible and use of opioid antagonists should be avoided. Thus far there is no significant study that shows it is unsafe for breast-feeding. Therefore, we would recommend continuation of breast-feeding while the mother is being treated with buprenorphine.

Induction

The initial dose of buprenorphine should be between 2 and 8 mg. The initial dose should not be greater than 8mg. The following factors must be taken into consideration when considering the initial dose of Buprenorphine:

1. Degree of tolerance to opioids. Patients with a low degree of tolerance to should be commenced on a dose of 2 or 4 mg. In instances where the doctor is uncertain of the degree of tolerance, the patient should commenced on a dose of 4 mg. Patients with high levels of tolerance should commence on 6 or 8 mg.
2. Extent of opioid withdrawal at the time of first buprenorphine dose. Patients experiencing considerable opioid withdrawal at the time of the first dose require higher doses of buprenorphine to alleviate withdrawal symptoms. Patients with little or no indication of opioid withdrawal at the time of the first dose should be prescribed a lower dose, or be asked to re-present at a later time as use of buprenorphine may precipitate they withdrawal syndrome (see rationale below).
3. The perceived likelihood of concurrent drug abuse, including alcohol consumption, unauthorized use of prescription sedative drugs (particularly benzodiazepines), or illicit drug use. In such instances, lower doses of buprenorphine should be prescribed, with frequent reviews.
4. Concurrent medical conditions (particularly impaired hepatic function and interactions with other medications) warrant the use of lower initial doses of buprenorphine with regular

monitoring.[75]

The first dose of buprenorphine should be administered at least 6 hours after last heroin or 12 hours after short acting prescription opioid use. Care should be taken by prescribing doctors, pharmacists and nursing staff, not to administer the first dose to a patient within 6 hours of heroin or opioid use, and especially not to patients intoxicated on opioids. If they do, the patient may experience precipitated opioid withdrawal, as the buprenorphine displaces heroin and opioids from the opioid receptors. Buprenorphine-precipitated withdrawal typically begins 1- 4 hours after the first buprenorphine dose, is generally mild to moderate in severity, and lasts for up to 12 hours. If this happens, patients may require symptomatic withdrawal medication. [78]

Subsequent doses of buprenorphine (taken the following day) should result in light or minimal withdrawal discomfort if the patient has not used heroin or opioids during the intervening period. Patients who continue to use heroin or opioids between their first and second doses of buprenorphine may have difficulty stabilizing on the treatment, with ongoing features of opioid withdrawal. They should be advised to cease heroin or short-acting opioids use at least 6 hours prior to the next dose of buprenorphine.

Transferring from methadone maintenance or long-acting opioid treatment: Buprenorphine has a higher affinity for μ opioid receptors than methadone and all other prescribed opioids, but a weaker action (lower intrinsic activity) at these receptors. When methadone/long-acting opioid patients take a dose of buprenorphine, the methadone/long-acting opioid is displaced from the μ-opioid receptors by buprenorphine. Patients on low doses of methadone (e.g. less than 30 mg) generally tolerate this transition with minimal discomfort. However, patients on higher doses of methadone may find the replacement of methadone with buprenorphine precipitates transient opioid withdrawal. This has a number of clinical implications. Wherever possible, patients in methadone treatment should have their

methadone dose reduced and should be stabilized on this low dose prior to transferring to buprenorphine, in order to minimize any opioid withdrawal features. The following table describes key factors in the development of precipitated withdrawal.[11, 12, 75]

KEY FACTORS AFFECTING PRECIPITATED WITHDRAWAL		
Factor	**Discussion**	**Recommended strategy**
Dose of methadone	Doses greater than 30 mg of methadone are more often associated with precipitated withdrawal. In general, the higher the methadone dose, the more severe the withdrawal experienced.	Attempt transfer from low dose of methadone (e.g. < 40 mg where possible). Patients on > 60 mg methadone should not attempt transfer.
Time between last methadone dose and first buprenorphine dose	Buprenorphine should not be taken within 24 hours of last methadone dose. Increasing the interval between last dose of methadone and first dose of buprenorphine reduces the incidence and severity of precipitated withdrawal.	Cease methadone and delay first dose of buprenorphine until patient is experiencing features of methadone withdrawal
Dose of buprenorphine	Very low doses of buprenorphine (e.g. 2 mg) are generally inadequate to substitute for methadone (unless the methadone dose is very low). High first doses of buprenorphine (e.g. 8 mg or more) are more likely to precipitate withdrawal, as there is greater displacement of methadone from the receptors. This is a common mistake by inexperienced prescribers.	First dose of buprenorphine should generally be 4 mg, with review of the patient 2 - 4 hours later (or early the following day)
Patient expectancy	Patients who are not prepared for the possibility of precipitated withdrawal are more likely to be distressed and confused by its onset, with potential negative consequences (e.g. treatment drop-out, abuse of other medications). Symptomatic medication (eg clonidine) can be useful in relieving any precipitated withdrawal.	Inform patients fully (and care givers where relevant). Provide written information. Prepare a contingency management plan for severe symptoms. Prescribe and dispense in accordance with a management plan

The following conversion rates can be be used when converting from low-dose methadone to

I Buprenorphine.

Last Oral Methadone Dose	**Initial Buprenorphine Dose**	**Day 2 Buprenorphine Dose**
(mg)	(mg) (S/L tablet)	(mg) (S/L tablet)
20 - 40 mg	4 mg	6 to 8 mg BID
10 - 20 mg	4 mg	4 to 8 mg QD-BID
1 - 10 mg	2 mg	2 to 4 mg Daily

The first dose of buprenorphine should be administered at least 24 hours after the last methadone or long-acting opioid dose, and at least 6 hours after last heroin use. The likelihood of precipitating withdrawal on commencing buprenorphine is reduced as the time interval between the last methadone dose and the first buprenorphine dose increases. A precipitated withdrawal may be avoided by ensuring the last dose of methadone/long-acting opioid is taken early in the morning, and the first dose of buprenorphine is taken late the following day. e.g. Last dose of methadone/long-acting opioid – early morning; 1st dose buprenorphine – late next day.

Features of a precipitated withdrawal following the first dose of buprenorphine are typically mild to moderate in severity, which can distress the unprepared patient. Symptoms commence 1 - 4 hours after the first buprenorphine dose and last for up to 12 hours before subsiding. Patients experiencing discomfort may re-present to the prescribing doctor later in the day and require symptomatic withdrawal medication (eg clonidine 0.1 mg 3 - 4 x day). Subsequent doses of buprenorphine (the following day) are less likely to precipitate withdrawal symptoms. Transferring to buprenorphine from doses of methadone greater than 40 mg (ie where there is a risk of relapse to heroin on lower dose) Most patients in methadone treatment require maintenance doses of greater than 40 mg of methadone

to achieve abstinence from heroin, and are unable to reduce their dose of methadone to 40 mg or less without considerable withdrawal discomfort or relapse to heroin use. As it may be difficult to get these patients' doses of methadone below 40 mg, transfer to buprenorphine may need to be considered at higher methadone doses, with the inherent risks associated with such a procedure explained fully to the patient. It is possible to transfer to buprenorphine from methadone doses of 40 - 60 mg for those patients who choose to do so. The general principle is to cease methadone dosing, and delay the initiation of buprenorphine treatment until the patient experiences significant, observable features of opioid withdrawal. This generally means that buprenorphine is not commenced until 48 - 96 hours after the last dose of methadone. Patients should be warned that the use of heroin or other opioids at this stage increases the likelihood of a difficult initiation to buprenorphine. Symptomatic withdrawal medication may be prescribed to ease the discomfort of methadone withdrawal, although the quantities of medications, such as benzodiazepines or clonidine, should be limited. Medications containing codeine or propoxyphene should be avoided. Prepare the patient for withdrawal symptoms. Patients should have the possibility of precipitated withdrawal explained, as well as the relevant strategies for dealing with its symptoms. Transfer should be organized for a time when the patient has no significant work or other commitments, and the doctor is available for review.[11, 12, 75]

Patients should be reviewed by their prescriber immediately prior to commencing buprenorphine, to ensure they are indeed in opioid withdrawal. The first dose of buprenorphine should be 2-4 mg. After first dose, later the same day (approximately 3 - 4 hours after the first dose of buprenorphine):

1. If patient is experiencing no increase in withdrawal severity, either subjectively or objectively, give another 2 or 4 mg of buprenorphine.
2. If patient is experiencing a worsening of withdrawal, give no further dose that day. Symptomatic withdrawal medication may be required for the rest of the day (eg clonidine 0.1 mg hourly).
3. Peak withdrawal discomfort is experienced during the first day of buprenorphine treatment.

Second day: Review by the prescriber prior to dosing on the following day. Dose can generally be increased to 6 or 8 mg.

Subsequent days: Subject to review of the patient by the prescriber, further increases. Patients may not feel entirely comfortable during the whole first week.

Maintenance

The optimal maintenance dose needs to be individualized according to the patient's response to buprenorphine. People's responses vary considerably, according to the following factors:

1. Rates of absorption or metabolism of buprenorphine
2. Levels of opioid tolerance and dependence
3. Experience of side-effects
4. Continued use of other drugs

These variations require the clinician to titrate the buprenorphine dose to optimize treatment objectives. Equilibrium levels with buprenorphine are achieved quickly, and the effects of a dose-change should become apparent within 2 - 3 days. Consequently, dose levels of buprenorphine can be more rapidly titrated according to patient response, than can methadone.

Regular patient review for first few weeks to evaluate adequacy of dose; withdrawal symptoms, side-effects, or any additional drug use. Increase dose only as indicated by reviews (see below for guidance on titration of doses)

Frequent reviews by the prescriber are required in the first few weeks:

1. To titrate the individual to achieve optimal doses of buprenorphine,
2. To make a more comprehensive overall assessment of the patient;
3. To further discuss treatment plans.

As treatment progresses, the prescribing doctor should review the patient 2-3 times a week until

stabilized:

1. To establish adequacy of dose;
2. To inquire about withdrawal symptoms or side-effects;
3. To monitor any additional drug use.

Maintenance buprenorphine doses should be achieved within the first one or two weeks of treatment, subject to the patient's use of heroin, or other drugs. The following minimal schedule of reviews is recommended for patients with a moderate to severe opioid use disorder:

1. The day after the first dose of buprenorphine. This enables the prescriber to identify the onset of any precipitated withdrawal and the general adequacy of the first dose.
2. Every 2 - 4 days until stabilization.
3. Every week during the following 4 – 6 weeks.
4. Every two weeks during the following 6 – 8 weeks.
5. Monthly reviews thereafter, although the prescriber may wish to extend reviews to up to 3 months for very stable patients.

In practice, a suitably trained advanced practice provider often undertakes these reviews, with reference to the prescribing doctor where necessary. Patient should see the physician at minimum every 90 days for medication review. Individuals with continuing high-risk patterns of drug use, or concomitant medical, psychiatric or social problems, may require more frequent review. Dose increases should be made only after review of the patient by the prescribing doctor. If daily reviews can be organized by the prescriber, daily increases can be accommodated. Practically, however, most prescribers may not be able to review the patient more than every two or three days. A period of 2 to 3 days on a specific dose allows the patient time to get a 'feel' for their current dose, and the opportunity to modify behavior appropriately prior to further dose changes. The buprenorphine dose may be decreased where there are concerns regarding the patient's safety (e.g. where there are reports of intoxication, diversion or

overdose).

Titrating the dose of buprenorphine

The dose response curve of buprenorphine indicates that small increments have a greater impact at low doses, whereas at higher doses, larger changes are required for a substantial change of effect. The following increments are proposed:

1. Below 16 mg buprenorphine: dose changes of 2 - 4 mg
2. Above 16 mg buprenorphine: dose changes of 4 - 8 mg.

At each review, the buprenorphine dose should be titrated according to the following parameters:

1. Features of intoxication or withdrawal over preceding 24 hours (self-report, examination);
2. Cravings for heroin use;
3. Additional drug use (heroin and other drugs), and reason stated by patient for using;
4. Side-effects or other adverse events (including intoxicated presentations, overdoses);
5. Adherence with dosing regimen (attendance for dosing, route of administration);
6. Patient satisfaction with buprenorphine dose and treatment.

Buprenorphine doses need to be individually titrated according to the patient's response to treatment. Effective maintenance doses, resulting in reduced heroin use and improved treatment retention, are achieved with high buprenorphine doses in the range of 12 - 24 mg per day. Some patients may be satisfactorily maintained on daily doses of 8 - 12 mg, while doses of 4 mg or less will not be as effective in retaining patients in treatment or reducing heroin use (similar to, or worse than, the outcomes associated with methadone doses of 20 mg). There is little evidence to suggest that daily doses higher than 24 mg will result in improved outcomes or effects, and little is known regarding the nature of adverse events at maintenance daily doses greater than 32 mg. The maximum daily dose of buprenorphine routinely recommended is 32 mg.[12, 75, 79, 80]

People wishing to reduce their craving of heroin, or other opioids, can do so with increases in the

substitution dose of buprenorphine, as higher doses of this substance produce more effective antagonist reactions, blocking the craving for the dopamine and related neurochemicals. However, this only succeeds up to a point. Continued heroin and opioid use despite adequate daily doses of buprenorphine may indicate that the patient needs more intensive psychosocial interventions, and/or an alternative opioid substitution (e.g. methadone or naltrexone).

All Take Home Doses

"Take-away" is medication not administered by the dispensing clinician, but given to the patient for administration at a later time. This is been an interesting dichotomy amongst primary care physicians who write this on an outpatient basis and opioid treatment providers to dose this daily not unlike daily methadone dosing. Many patients will start their journey at the methadone clinic only to voluntarily leave because they found an outpatient provider willing to write for one month at a time. Therefore, it may be beneficial to allow for earlier take home doses of buprenorphine. A patient who has a mild form of and opioid use disorder may be able to start take home doses right away. However, I know you this does not change the need for appropriate scheduled and regular behavioral therapy. This also does not change the need for regular and ongoing urine drug testing. As we develop a better understanding about the natural history of moderate to severe opioid use disorder patients who are on buprenorphine we will be able to better delineate the most effective timing for regular take home doses. Stable methadone patients transferring from methadone will be eligible for take-away dose(s) under the same circumstances once they are stable on buprenorphine without the need to wait an additional two months. The benefits of take-away opioid doses:

1. They emphasize and promote patients' responsibility for their own treatment;
2. They enhance the patients' integration into the community by cutting time and travel costs associated with the treatment;
3. They tend to promote patient retention by minimizing the inconvenience of regular attendance

for doses. (Studies show take-away policies produce better retention rates than programs which restrict take-away doses).

4. They benefit opioid treatment programs by reducing the inconvenience and cost of daily it dispensing.

Withdrawal from buprenorphine maintenance treatment

There is some clinical and anecdotal evidence that withdrawal from buprenorphine is less prolonged and less severe than methadone withdrawal, but the research on this is not conclusive. Withdrawal does appear to be milder during buprenorphine dose reductions, and the rate of buprenorphine dose-reduction is normally more rapid than with methadone. The symptoms and signs of withdrawal from buprenorphine are qualitatively similar to withdrawal from other opioids.

Common pattern of long-term withdrawal of buprenorphine treatment:

1. The onset of symptoms is usually around 24 - 72 hours after the last 24-hour dose.
2. Symptoms peak around days 3 - 5 following short maintenance courses of buprenorphine treatment (weeks / months), or days 5 - 14 for longer-term treatment.
3. Duration of withdrawal from buprenorphine maintenance treatment has not been established, although mild to moderate withdrawal symptoms (particularly cravings, sleep and mood disturbances associated with protracted withdrawal) are likely to persist for weeks. One study described mild but ongoing withdrawal features 30 days after the last buprenorphine dose. Longer-term follow up has not been reported.

Voluntary withdrawal from buprenorphine maintenance treatment

Evidence from methadone research suggests that long-term outcomes of treatment are enhanced by:

1. Longer treatment episodes. Evidence from methadone research suggests that long-term outcomes are enhanced by longer treatment episodes (for example, more than 36 months).

2. A more stable and supportive lifestyle. The longer treatment episode allows the opportunity for the patient to establish a lifestyle away from heroin and other drug use prior to withdrawing from methadone treatment. Premature withdrawal from methadone (before the patient has achieved a degree of stability in social circumstances and drug use) is more likely to be associated with a relapse into dependent heroin use.

The likelihood of premature withdrawal from maintenance treatment is reduced by:

1. A well-informed patient, with all the facts about the maintenance program. A patient may wish to withdraw from maintenance treatment for a range of reasons, e.g. the need for interstate travel, concerns about side-effects or about remaining in treatment 'too long'. The clinician should address issues regarding the duration of treatment and withdrawal early in the treatment program, and provide information regarding the process of withdrawal. Patient literature is now available regarding withdrawal from methadone treatment (Dunlop et al 1996), and parallels can be made with withdrawal from buprenorphine. Despite withdrawal from buprenorphine being frequently described as milder than from other opioids, patients should be informed of the likely withdrawal profile. Except in the case of involuntary withdrawal (see below), withdrawal from buprenorphine should occur only with the consent of the patient. Graduated reduction over weeks results in better outcomes (less relapse to heroin use) than rapid reductions.

Involuntary withdrawal

As stated in the methadone chapter there are only three reasons for withdrawal from buprenorphine maintenance treatment. The first would be, the patient who has been stable for 2 to 3 years and is attempting to taper down so that they may become drug-free. The second would be a failure of buprenorphine as the drug of choice for medication assisted treatment. And the third would be significant and persistent aberrant behavior that has been refractory to correction. Removing a patient

from buprenorphine maintenance treatment without a plan for continued care will lead to early relapse with an increase in mortality rate for this population. If the above issues have arisen then patient should be set forward with one of two general pathways. The first would be a more rapid taper which could be for patients who will become incarcerated or otherwise need to be in a drug-free environment. This can be done by a 2 mg per day decrease in the dose of buprenorphine, the utilization of clonidine as well as gabapentin or benzodiazepines can be necessary. The second is a more prolonged and controlled weaning which would be decreasing by 2 mg every week. This may also include utilization of clonidine, but should not require other adjunctive medication such as gabapentin or benzodiazepines. The immediate cessation of buprenorphine except in the most extenuating circumstances should be considered unethical.

XIII. Naltrexone

Naltrexone (Nalorex, Bristol-Myers Squibb Pharmaceuticals Ltd or Vivitrol, Alkermes) is an opioid antagonist with a high affinity for opioid receptors. It competitively displaces opioid agonists, blocking the euphoric and other effects of opioids and thereby minimizing the positive rewards associated with their use. The 'Summary of product characteristics' (SPC) states that naltrexone is licensed for use as an adjunctive prophylactic treatment for detoxified formerly opioid-dependent patients (who have remained opioid free for at least 7–10 days). There are both oral preparations as well as an intramuscular depot preparation.

Oral Naltrexone is rapidly absorbed, metabolized by the liver and excreted in the urine with an elimination half-life of 4 hours. Liver function tests are recommended before and during naltrexone treatment to check for liver impairment. The SPC states that 'caution should be observed in administering the drug to patients with impaired hepatic or renal function'. This medication can be dosed had 50 mg daily or may also be taken three times weekly dosing with two 100 mg doses followed by one 150 mg dose. The intramuscular injection is housed in a polymer microsphere and is released in phases via diffusion and polymer erosion. The initial phases within the first 24 hours and releases the drug located on the surface at the injection site. Once the injection site undergoes hydration which typically happens within 48 hours sustained-release phase occurs over the next 30 days. There does not appear to be a weight dependent nor first pass metabolism impact.[8, 9, 39]

Naltrexone is associated with opioid withdrawal symptoms if people are opioid dependent. The summary of product characteristics recommends challenge testing with naloxone hydrochloride (a shorter-acting injectable opioid antagonist) to screen for the presence of opioids if it is not certain whether the patient has been adequately detoxified. The vast majority of research to date shows that

this is a highly effective treatment for opioid use disorders in patients who either have contraindications to, have failed pharmacotherapy with buprenorphine and methadone or have been in a confined drug-free situations such as jail or inpatient rehabilitation or individuals who are highly motivated in their recovery and are willing to detox outpatient offer their current agonist therapy.

This medication can be prescribed by any physician, however is highly recommended that the patient also be involved in concomitant behavioral therapy to support recovery. When this medication is stopped there is no associated withdrawal syndrome. However, generally speaking any patient who has been on this medication will be much more hypersensitive to any opioid being used. Therefore, overdose risk is very high if the patient relapses to opioids and thus the patient should be educated about all risks and benefits of this medication. Patient should be engaged at or near the end of the timeframe for injection. Patient should have oral naltrexone prescribed in case they are unable to arrive for the next 30 days injection. Would highly recommend intensifying or scheduling behavioral therapy appointments close to the time in which the next injection would be required.[81]

XIV. Special Considerations During Pregnancy

Treating an opioid use disorder in a patient during pregnancy presents more challenges, risks and often greater reward than that of a standard patient. However, the disease of addiction in the pregnant patient is no different than a non-pregnant patient. And while the subtleties of drug dosing may be different as discussed below the overriding theme of utilizing medication assisted treatment in association with psychosocial interventions is of the utmost importance. Three things can make it difficult to initially stabilize the mother with an opioid use disorder.[82] The first is the all-encompassing shame and guilt that a mother-to-be feels about having active addiction while pregnant. This significantly impedes and delays disclosure of the problem and in many cases may lead to lack of prenatal care altogether. This is why it is important that patients are screened with a standardized tool at the first or second OB/GYN visit and at minimum drug screened in the first and third trimester for illicit substances. If addiction is suspected or confirmed, compassionate, nonjudgmental intervention and help should be offered without barrier. The second difficulty is the lack of education for both the patient's and in many cases their family on the benefits of medication assisted treatment during pregnancy. Explaining to the family and the patient that the utilization of methadone or buprenorphine during pregnancy has not shown any long-term negative effects on the unborn child. The highest risk to the unborn child is acute opioid withdrawal and/or untreated addiction. This coupled with an in depth explanation of neonatal abstinence syndrome and how there are no long-term repercussions of this will help the patient, the father of the baby as well as the family feel more comfortable with treatment and thus more likely to follow through. The third and possibly the most important is a lack of access to adequate treatment for pregnant individuals. Many of these patients live in rural areas that do not have methadone clinics available or physicians who feel comfortable utilizing buprenorphine-naloxone during pregnancy. Below we will attempt to increase the level of comfort for physicians as well as provide

information which can be used to educate the patient's and their families prior to initiation and continuation of treatment.

Methadone

Methadone has long been the standard of care for the treatment of opioid use disorder in pregnant patients. This is because it allows for a transition onto maintenance dosing with a lower risk of any withdrawal symptoms and provides close monitoring of the patient's involved in the methadone clinic. Many studies have shown significant improvement and outcomes of both the mother and the unborn child when the patient is engaged in medication assisted treatment with methadone.[83] This includes less risk of contracting communicable diseases, less chance of relapse, less chance of criminal behavior and a better chance of term delivery.

The induction and maintenance phase of methadone for pregnant patient is no different than that described in the methadone section of the guidelines. These patients will generally level out at the same 90-120 mg dose that non-pregnant patients will.[84] However, due to an increase in metabolism during pregnancy some females may require a 15% increase in total dosing and/or the addition of split dosing. Split dosing should be attempted prior to an increase in dose. Split dosing with 70% of the dose in the morning and 30% of the dose in the evening provides better initial craving cessation during the day and continuation of stability throughout the evening, which prevents withdrawal symptoms prior to the next morning's dose. The 70-30 split seems to be more effective than the 50-50 split with an overall lower total dose requirement. With the exception of the extremes in dose there does not appear to be a direct relation between total dose of methadone taken by the mother and risk of neonatal abstinence syndrome.

Methadone-Treatment during Delivery and Post-Partum

Treatment of the patient in the hospital is relatively straightforward with methadone. This includes maintaining the daily dose regimen of methadone, relatively normal utilization of epidural and spinal analgesia and treatment of postpartum pain in the usual fashion. The caveats to this are instructing the labor and delivery team to not increase methadone in order to treat acute pain and that the baseline opioid requirements of these patients for pain relief may be 15 to 20% higher than that of a person not on methadone. They should also be instructed to inform the methadone clinic of any controlled substance prescriptions written for the patient's discharge.

Patient example: 23 y/o on 120 mg of methadone daily that is split dosed at 90 mg in the am and 30 mg in the pm.

Spontaneous vaginal delivery:

- Continue methadone at 90mg am and 30mg PM
- May use epidural per usual (may require increase of 15-20% in opioid dose)
- Add Ketorolac 15-30mg IV every 6-8 hours or Ibuprofen 800mg every 8 hours
- Discharge on same dose of methadone and make sure patient can dose the day after discharge

C-section Delivery:

- Continue methadone at 90mg am and 30mg PM
- Spinal analgesia per usual
- Add Ketorolac 15-30mg IV every 6-8 hours or Ibuprofen 800mg every 8 hours
- If still painful would use Patient Controlled Analgesia (PCA) at 150 mcg/4 hours with no basal rate for 36-48 hours

- May add 1 gram of IV acetaminophen Q 6 hours
- Discharge on 3 days of short acting opioid and call the methadone clinic to obtain insight and provide appropriate care transition

Methadone-Breast Feeding

Currently there is no contraindication for breast-feeding while taking methadone. This may also significantly decrease neonatal abstinence severity and duration. The mother should be encouraged to breast-feed given all of the known nutritional benefits as well as the increased difficulty for mother baby bonding in a patient with the disease of addiction.[85]

Buprenorphine

The 2012 MOTHER study showed a significant decrease in both the severity and duration of neonatal abstinence syndrome in neonates whose mothers utilized buprenorphine during pregnancy when compared to methadone during pregnancy. [86]Office-based buprenorphine treatment also provides for a greater degree of freedom in patients who are motivated to continue in treatment. However, it may be difficult to transition a patient off of the opioid being abused onto buprenorphine. Given that acute opioid withdrawal is one of the more significant risks during pregnancy care should be taken to avoid this if at all possible. There are two transition strategies being evaluated now. These include utilizing transdermal buprenorphine for transition to buprenorphine – naloxone as well as bridging the patient on Fentanyl to a low dose of buprenorphine. Neither of these should be considered standard of care, but if utilized the mother should be monitored closely during the transition. Once the mother is on a stable maintenance dose there does not appear to be a need to increase the dose secondary to

metabolic changes in the pregnant mother. It is however, recommended that at minimum two times a day dosing be utilized to mitigate the risk of end of dose withdrawal.

Currently the state of Michigan provides only buprenorphine – naloxone for pregnant patients. This is secondary to there is no compelling data to show an increased risk for using the combination product as compared to buprenorphine alone. This was also adopted following the ongoing reports of diversion and abuse of Subutex.

Buprenorphine-Treatment during Delivery and Post-Partum

Treatment of pain during delivery and postpartum in a patient on buprenorphine has been heavily debated over the last few years. The following are recommendations based on decrease risk of withdrawal, improved pain treatment during labor and post C-section, as well as ease of transition back to maintenance dosing after discharge. Taking into account the difficulty of transitioning a patient after a hospital stay it is important that the patient be maintained on their buprenorphine during delivery and the postpartum phase. This can be done by decreasing the total dose to no more than 8 mg daily and utilizing fentanyl as the opioid treatment of choice. Given that Fentanyl has an almost equal affinity for the mu receptor and is highly potent, this medication can overcome buprenorphine's effects. It would be recommended that if the patient receives an epidural that fentanyl be used in the epidural rather than morphine. If the patient receives spinal analgesia fentanyl could/should be used in the place of other opioid analgesics. For a patient who has an uneventful spontaneous vaginal delivery the utilization of nonsteroidal anti-inflammatory drugs such as ketorolac or ibuprofen are the standard of care. In this case the patient can immediately be placed back on her daily regimen of buprenorphine. If the patient has a significant tear during delivery the patient may require 24 to 36 hours of fentanyl delivered through patient controlled analgesia. If the patient requires C- section then the patient's may receive 48

hours of fentanyl based patient controlled analgesia as well as utilization of nonsteroidal anti-inflammatory medications. 1 g of IV acetaminophen Q6 hours may also be added. This medication is safe and has been shown to significantly decrease opioid requirements in postoperative patients. For continued treatment of the pain after C-section, we recommend an increase in the dose of buprenorphine up to 24 mg per day for five days post-delivery and then an appropriate return to pre-delivery dosing for maintenance.

Patient example: 23 y/o on 8mg of buprenorphine-naloxone 2 times per day (BID)

Spontaneous vaginal delivery:

- Decrease Buprenorphine to 8 mg daily
- May use epidural but would use fentanyl as opioid
- Add Ketorolac 15-30mg IV every 6-8 hours or Ibuprofen 800mg every 8 hours
- After 36 hours return to 8mg of Buprenorphine-naloxone BID
- Discharge on same dose with no further opioid prescriptions

C-section Delivery:

- Decrease buprenorphine to 8mg daily
- Spinal analgesia using fentanyl as the opioid
- Add Ketorolac 15-30mg IV every 6-8 hours or Ibuprofen 800mg every 8 hours
- If still painful would use Patient Controlled Analgesia (PCA) at 150 mcg/4 hours with no basal rate for 36-48 hours
- May add 1 gram of IV acetaminophen Q 6 hours
- Increase buprenorphine-naloxone to 8 mg 3 times per day and call provider to obtain insight and provide appropriate care transition

Buprenorphine-Breast Feeding

Currently there is no contraindication for breast-feeding in a patient on buprenorphine maintenance. This may also significantly decrease the risk of neonatal abstinence syndrome and provides for a better mother baby bonding potential as delineated above.

Naltrexone

Currently naltrexone is contraindicated for use in a pregnant patient. If the patient is on oral naltrexone and becomes pregnant, cessation of this medication is appropriate. However, it would also be appropriate to consider utilization of low-dose agonist therapy in its place if the patient has a significant return of symptoms or an increase in the severity of their disease.[87] Prior to initiating agonist therapy it would be prudent to attempt to utilize an increase in behavioral therapy to determine if this is adequate. However, relapse is not required to start the patient on agonist therapy. Only a perceived or actual worsening of the disease. It is well-documented that patients not receiving medication assisted therapy for an opioid use disorder have a higher risk of relapse. Thus, the risk to the neonate on a low dose of buprenorphine – naloxone as compared to relapse is much lower. Each individual should be monitored closely for disease severity as well as consistency of urine toxicology studies. If the patient had received an injection of depot naltrexone and became pregnant (always do a pregnancy test prior to injection) the next injection should not be given and the above instructions should be followed. It is also important that this information be sent to the makers of depot naltrexone as this will help to determine safety of use during pregnancy.

Key Points:

- Under no circumstances should a pregnant patient be forcefully weaned off of medication assisted therapy. This includes incarceration.
- Buprenorphine has shown improved outcomes for the neonate when compared to methadone.

- Methadone is still the gold standard given its long history of use, decreased risk of withdrawal and high intensity treatment pathway.
- Patients should be maintained on buprenorphine and methadone while hospitalized for delivery
- Methadone dose may need to be increased during pregnancy, however, consideration should be made for split dosing prior to an increase in dose.
- Methadone should not be used for acute pain treatment in the hospital
- Breastfeeding is safe with both buprenorphine-naloxone and methadone[86, 88]

XV. Bibliography

1. Statement, A.P.P., *The Definition of Addiction*, 2011, American Society of Addiction Medicine.
2. Association, A.P., ed. *Diagnostic and statistical manual of mental disorders*. 5th ed ed. 2013, American Psychiatric Publishing: Arlington, VA.
3. Kobra, L., B.N. Mohammad, and S.S. Alireza, *Quality of life in patients on methdone maintenance treatment: A three-month assessment.* The Journal of the Pakistan Medical Association, 2012. **62**(10): p. 1003-1007.
4. Alavian, S.M., et al., *Effectiveness of Methadone Maintenance Treatment in Prevention of Hepatitis C Virus Transmission among Injecting Drug Users.* Hepatitis Monthly, 2013. **13**(8): p. e12411.
5. Bell, J., et al., *A pilot study of buprenorphine-naloxone combination tablet (Suboxone) in treatment of opioid dependence.* Drug and Alcohol Review, 2004. **23**: p. 311-317.
6. Maremmani, I.M. and G.M. Gerra, *Buprenorphine-Based Regimens and Methadone for the Medical Management of Opioid Dependence: Selecting the Appropriate Drug for Treatment.* The American Journal on Addictions, 2010. **19**(6): p. 557-568.
7. Polsky, D.P., et al., *Cost-effectiveness of Extended Buprenorphine-Naloxone Treatment for Opioid-Dependent Youth: Data from a Randomized Trial.* Addiction, 2010. **105**(9): p. 1616-1624.
8. Kjome, K.L. and F.G. Moeller *Long-Acting Injectable Naltrexone for the Management of Patients with Opioid Dependence*. Substance Abuse: Research and Treatment, 2011. **5**, 1-9.
9. Comer, S.D.P., et al., *Injectable, Sustained-Release Naltrexone for the Treatment of Opioid Dependence.* Archives of General Psychiatry, 2006. **63**(2): p. 210-218.
10. Stitzer, M., N. Petry, and J. Peirce, *Motivational incentives research in the National Drug Abuse Treatment Clinical Trials Network.* Journal of Substance Abuse Treatment, 2010. **38**(Suppl 1): p. S61-S69.
11. Organization, W.H., *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence*, M. Davoli, Editor 2009, WHO Press, World Health Organization,: Geneva 27, Switzerland. p. 136.
12. Vermont, S.o., *Vermont buprenorphine practice guidelines*, O.o.V.h. access, Editor 2010. p. 57.
13. Brands, B., et al., *Prescription opioid abuse in patients presenting for methadone maintenance treatment.* Drug and alcohol dependence, 2004. **73**(2): p. 199-207.
14. Clark, R.E., et al., *The Evidence Doesn't Justify Steps By State Medicaid Programs To Restrict Opioid Addiction Treament With Buprenorphine.* Health Affairs, 2011. **30**(8): p. 1425-1433.
15. Panel, A.S.o.A.M.s.A.P.I.a.P.M.A.G.P.a.i.S.a.O.o.C.E., *Standards of Care: for the Addiction Specialist Physician*, M. Jarvis, Editor 2013, American Society of Addiction Medicine.
16. Young, M.M., et al., *Effectiveness of brief interventions as part of the screening, brief intervention and referral to treatment (SBIRT) model for reducing the non-medical use of psychoactive substances: a systematic review protocol.* Systematic reviews, 2012. **1**: p. 22.
17. Webster, L.R. and R.M. Webster, *Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool.* Pain medicine, 2005. **6**(6): p. 432-42.
18. Butler, S.F., et al., *Development and validation of the Current Opioid Misuse Measure.* Pain, 2007. **130**(1-2): p. 144-56.
19. Yudko, E., O. Lozhkina, and A. Fouts, *A comprehensive review of the psychometric properties of the Drug Abuse Screening Test.* Journal of substance abuse treatment, 2007. **32**(2): p. 189-98.
20. Skinner, H.A., *The drug abuse screening test.* Addictive behaviors, 1982. **7**(4): p. 363-71.
21. Oden, N.L., et al., *Power of automated algorithms for combining time-line follow-back and urine*

drug screening test results in stimulant-abuse clinical trials. The American journal of drug and alcohol abuse, 2011. **37**(5): p. 350-7.
22. Denis, C.M., J.S. Cacciola, and A.I. Alterman, *Addiction Severity Index (ASI) summary scores: comparison of the Recent Status Scores of the ASI-6 and the Composite Scores of the ASI-5.* Journal of substance abuse treatment, 2013. **45**(5): p. 444-50.
23. Kosten, T.R., B.J. Rounsaville, and H.D. Kleber, *Concurrent validity of the addiction severity index.* The Journal of nervous and mental disease, 1983. **171**(10): p. 606-10.
24. McLellan, A.T., et al., *An improved diagnostic evaluation instrument for substance abuse patients. The Addiction Severity Index.* The Journal of nervous and mental disease, 1980. **168**(1): p. 26-33.
25. Rikoon, S.H., et al., *Predicting DSM-IV dependence diagnoses from Addiction Severity Index composite scores.* Journal of substance abuse treatment, 2006. **31**(1): p. 17-24.
26. Strain, E.C.M., et al., *Buprenorphine Versus Methadone in the Treatment of Opioid Dependence: Self-Reports, Urinalysis, and Addiction Severity Index.* Journal of Clinical Psychopharmacology, 1996. **16**(1): p. 58-67.
27. Tompkins, D.A., et al., *Concurrent validation of the Clinical Opiate Withdrawal Scale (COWS) and single-item indices against the Clinical Institute Narcotic Assessment (CINA) opioid withdrawal instrument.* Drug and alcohol dependence, 2009. **105**(1-2): p. 154-9.
28. El-Sheikh Sel, G. and T.Z. Bashir, *High-risk relapse situations and self-efficacy: comparison between alcoholics and heroin addicts.* Addictive behaviors, 2004. **29**(4): p. 753-8.
29. Hulse, G.K., H.T. Ngo, and R.J. Tait, *Risk factors for craving and relapse in heroin users treated with oral or implant naltrexone.* Biological psychiatry, 2010. **68**(3): p. 296-302.
30. Robertson, J.R., et al., *Remission and relapse in heroin users and implications for management: treatment control or risk reduction.* The International journal of the addictions, 1989. **24**(3): p. 229-46.
31. Jones, K.L. and G.A. Barr, *Injections of an opioid antagonist into the locus coeruleus and periaqueductal gray but not the amygdala precipitates morphine withdrawal in the 7-day-old rat.* Synapse, 2001. **39**(2): p. 139-51.
32. Scavone, J.L. and E.J. Van Bockstaele, *Mu-opioid receptor redistribution in the locus coeruleus upon precipitation of withdrawal in opiate-dependent rats.* Anatomical record, 2009. **292**(3): p. 401-11.
33. Tokuyama, S., et al., *The role of glutamate in the locus coeruleus during opioid withdrawal and effects of H-7, a protein kinase inhibitor, on the action of glutamate in rats.* Journal of biomedical science, 1998. **5**(1): p. 45-53.
34. Dehpour, A.R., et al., *Clonidine attenuates naloxone-induced opioid-withdrawal syndrome in cholestatic mice.* Pharmacology & toxicology, 2001. **89**(3): p. 129-32.
35. Kienbaum, P., J. Peters, and N. Scherbaum, *Convincing effects of clonidine on neurohumoral withdrawal symptoms during antagonist-supported detoxification of opioid addicts.* Anesthesia and analgesia, 2003. **97**(5): p. 1547-8; author reply 1547-8.
36. Malek, A., S. Amiri, and B. Habibi Asl, *The therapeutic effect of adding dextromethorphan to clonidine for reducing symptoms of opioid withdrawal: a randomized clinical trial.* ISRN psychiatry, 2013. **2013**: p. 546030.
37. Uhde, T.W., D.E. Redmond, Jr., and H.D. Kleber, *Clonidine suppresses the opioid abstinence syndrome without clonidine-withdrawal symptoms: a blind inpatient study.* Psychiatry research, 1980. **2**(1): p. 37-47.
38. Umbricht, A., et al., *Opioid detoxification with buprenorphine, clonidine, or methadone in hospitalized heroin-dependent patients with HIV infection.* Drug and Alcohol Dependence, 2003.

69: p. 263-272.
39. Syed, Y.Y. and G.M. Keating, *Extended-Release Intramuscular Naltrexone (VIVITROL): A Review of Its Use in the Prevention of Relapse to Opioid Dependence in Detoxified Patients.* CNS Drugs, 2013. **27**(10): p. 851-861.
40. Beck, A.T. and D.J. Dozois, *Cognitive therapy: current status and future directions.* Annual review of medicine, 2011. **62**: p. 397-409.
41. Beck, J.S., Beck, Aaron T., *Cognitive Behavior Therapy Basics and Beyond*2011, New York London: The Guilford Press.
42. McHugh, R.K., Hearon, Bridget A., Otto, Michael W., *Cognitive-Behavioral Therapy for Substance Use Disorders.* The Psychiatric Clinis of North America, Sep 2010: p. 511-525.
43. Miller, W.R., Rollnick, S., *Quick links about Motivational interview*, in *Motivational Interview*
44. Roll, J.M., Madden, Gregory J., Rawson, Richard, Petry, Nancy M., *Facilitating the adoption of Contigency Managment for the Treatment of Substance Use Disorders.* Behavioral Analysis in Practice, 2009: p. 4-13.
45. Galanter, M., et al., *Abstinence from drugs of abuse in community-based members of Narcotics Anonymous.* Journal of studies on alcohol and drugs, 2013. **74**(2): p. 349-52.
46. Krentzman, A.R., et al., *How Alcoholics Anonymous (AA) and Narcotics Anonymous (NA) Work: Cross-Disciplinary Perspectives.* Alcoholism treatment quarterly, 2010. **29**(1): p. 75-84.
47. Orwat, J., et al., *Factors associated with attendance in 12-step groups (Alcoholics Anonymous/Narcotics Anonymous) among adults with alcohol problems living with HIV/AIDS.* Drug and alcohol dependence, 2011. **113**(2-3): p. 165-71.
48. Eap, C.B., T. Buclin, and P. Baumann, *Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence.* Clinical pharmacokinetics, 2002. **41**(14): p. 1153-93.
49. Manfredonia, J.F., *Prescribing methadone for pain management in end-of-life care.* The Journal of the American Osteopathic Association, 2005. **105**(3 Suppl 1): p. S18-21.
50. Rajaratnam, R., et al., *The aging methadone maintenance patient: treatment adjustment, long-term success, and quality of life.* Journal of opioid management, 2009. **5**(1): p. 27-37.
51. Firoz, S. and G. Carlson, *Characteristics and treatment outcome of older methadone-maintenance patients.* The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry, 2004. **12**(5): p. 539-41.
52. Schmittner, J., et al., *Menstrual cycle length during methadone maintenance.* Addiction, 2005. **100**(6): p. 829-36.
53. Tuchman, E., *Exploring the prevalence of menopause symptoms in midlife women in methadone maintenance treatment.* Social work in health care, 2007. **45**(4): p. 43-62.
54. Tuchman, E., *Menopause symptom attribution among midlife women in methadone treatment.* Social work in health care, 2010. **49**(1): p. 53-67.
55. Tuchman, E., et al., *Relationship between menopause symptoms and HIV risk among midlife women in methadone treatment: a pilot study.* Substance use & misuse, 2013. **48**(9): p. 711-8.
56. Cornish, R., et al., *Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database.* BMJ, 2010. **341**: p. c5475.
57. Degenhardt, L., et al., *Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved.* Drug and alcohol dependence, 2009. **105**(1-2): p. 9-15.
58. Caplehorn, J.R. and O.H. Drummer, *Mortality associated with New South Wales methadone programs in 1994: lives lost and saved.* The Medical journal of Australia, 1999. **170**(3): p. 104-9.

59. Zador, D. and S. Sunjic, *Deaths in methadone maintenance treatment in New South Wales, Australia 1990-1995.* Addiction, 2000. **95**(1): p. 77-84.
60. Albion, C., M. Shkrum, and J. Cairns, *Contributing factors to methadone-related deaths in Ontario.* The American journal of forensic medicine and pathology, 2010. **31**(4): p. 313-9.
61. Bao, Y.P., et al., *A meta-analysis of retention in methadone maintenance by dose and dosing strategy.* The American journal of drug and alcohol abuse, 2009. **35**(1): p. 28-33.
62. Strain, E.C.M., et al., *Moderate- vs High-Dose Methadone in the Treatment of Opioid Dependence.* The Journal of the American Medical Association, 1999. **281**(11): p. 1000-1005.
63. Mohamad, N., et al. *Better retention of Malaysian opiate dependents treated with high dose methadone in methadone maintenance therapy*. Harm Reduction Journal, 2010. **7:30**.
64. Faggiano, F., et al., *Methadone maintenance at different dosages for opioid dependence.* The Cochrane database of systematic reviews, 2003(3): p. CD002208.
65. Abramson, D.W., D.K. Quinn, and T.A. Stern, *Methadone-Associated QTc Prolongation: A Case Report and Review of the Literature.* Primary care companion to the Journal of clinical psychiatry, 2008. **10**(6): p. 470-6.
66. Anchersen, K., et al., *Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: a mortality assessment study.* Addiction, 2009. **104**(6): p. 993-9.
67. Byrne, A., *Concerns about consensus guidelines for QTc interval screening in methadone treatment.* Annals of internal medicine, 2009. **151**(3): p. 216; author reply 218-9.
68. Dahan, A., et al., *Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats.* British journal of anaesthesia, 2005. **94**(6): p. 825-34.
69. Yassen, A., et al., *Pharmacokinetic-pharmacodynamic modeling of the antinociceptive effect of buprenorphine and fentanyl in rats: role of receptor equilibration kinetics.* The Journal of pharmacology and experimental therapeutics, 2005. **313**(3): p. 1136-49.
70. Griessinger, N., R. Sittl, and R. Likar, *Transdermal buprenorphine in clinical practice--a post-marketing surveillance study in 13,179 patients.* Current medical research and opinion, 2005. **21**(8): p. 1147-56.
71. Leander, J.D., *Buprenorphine is a potent kappa-opioid receptor antagonist in pigeons and mice.* European journal of pharmacology, 1988. **151**(3): p. 457-61.
72. Boas, R.A. and J.W. Villiger, *Clinical actions of fentanyl and buprenorphine. The significance of receptor binding.* British journal of anaesthesia, 1985. **57**(2): p. 192-6.
73. Bickel, W.K., et al., *Buprenorphine: dose-related blockade of opioid challenge effects in opioid dependent humans.* The Journal of pharmacology and experimental therapeutics, 1988. **247**(1): p. 47-53.
74. Bickel, W.K., et al., *A clinical trial of buprenorphine: comparison with methadone in the detoxification of heroin addicts.* Clinical pharmacology and therapeutics, 1988. **43**(1): p. 72-8.
75. Oros, M. and C. Welsh, *The Baltimore buprenorphine initiative: clinical guidelines for buprenorphine treatment of opioid dependence in the Baltimore buprenorphine initiative*, B.c.h. department, Editor 2011: Baltimore. p. 92.
76. Jones, H.E., et al., *Neonatal outcomes and their relationship to maternal buprenorphine dose during pregnancy.* Drug and alcohol dependence, 2014. **134**: p. 414-7.
77. O'Connor, A.B., et al., *Breastfeeding rates and the relationship between breastfeeding and neonatal abstinence syndrome in women maintained on buprenorphine during pregnancy.* Journal of midwifery & women's health, 2013. **58**(4): p. 383-8.
78. Doolittle, B.M., MDiv. and W.M. Becker, *A Case Series of Buprenorphine/Naloxone Treatment in a Primary Care Practice.* Substance Abuse 2011. **32**: p. 262-265.

79. Hser, Y.-I., et al., *Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial.* Addiction, 2014. **109**(1): p. 79-87.
80. Ling, W., et al., *From Research to the Real World: Buprenorphine in the Decade of the Clnical Trials Network.* Journal of Substance Abuse Treatment, 2010. **38**(Suppl 1): p. S53-S60.
81. Sigmon, S.C.P., et al., *Opioid Detoxification and Naltrexone Induction Strategies: Recommendations for Clinical Practice.* The American Journal of Drug and Alcohol Abuse, 2012. **38**(3): p. 187-199.
82. Jones, H.E., L.P. Finnegan, and K. Kaltenbach, *Methadone and buprenorphine for the management of opioid dependence in pregnancy.* Drugs, 2012. **72**(6): p. 747-57.
83. Lund, I.O., et al., *Comparing methadone and buprenorphine maintenance with methadone-assisted withdrawal for the treatment of opioid dependence during pregnancy: maternal and neonatal outcomes.* Substance abuse and rehabilitation, 2012. **3**(Suppl 1): p. 17-25.
84. Shiu, J.R. and M.H. Ensom, *Dosing and monitoring of methadone in pregnancy: literature review.* The Canadian journal of hospital pharmacy, 2012. **65**(5): p. 380-6.
85. Stack, D.M., et al., *The quality of the mother-child relationship in high-risk dyads: application of the Emotional Availability Scales in an intergenerational, longitudinal study.* Development and psychopathology, 2012. **24**(1): p. 93-105.
86. Bandstra, E.S., *Maternal Opioid Treatment: Human Experimental Research (MOTHER) Study: maternal, fetal and neonatal outcomes from secondary analyses.* Addiction, 2012. **107 Suppl 1**: p. 1-4.
87. Hulse, G.K., et al., *Naltrexone implant and blood naltrexone levels over pregnancy.* The Australian & New Zealand journal of obstetrics & gynaecology, 2003. **43**(5): p. 386-8.
88. Ding, Y.H., et al., *Study of mother-infant attachment patterns and influence factors in Shanghai.* Early human development, 2012. **88**(5): p. 295-300.