EXECUTIVE SECRETARY
KARL R. HADE

ASSISTANT EXECUTIVE SECRETARY &
LEGAL COUNSEL
EDWARD M. MACON

COURT IMPROVEMENT PROGRAM
SANDRA L. KARISON, DIRECTOR

EDUCATIONAL SERVICES
CAROLINE E. KIRKPATRICK, DIRECTOR

FISCAL SERVICES
JOHN B. RICKMAN, DIRECTOR

HUMAN RESOURCES
RENÉE FLEMING MILLS, DIRECTOR

SUPREME COURT OF VIRGINIA

OFFICE OF THE EXECUTIVE SECRETARY
100 NORTH NINTH STREET
RICHMOND, VIRGINIA 23219-2334
(804) 786-6455

JUDICIAL INFORMATION TECHNOLOGY
ROBERT L. SMITH, DIRECTOR

JUDICIAL PLANNING
CYRIL W. MILLER, JR., DIRECTOR

JUDICIAL SERVICES
PAUL F. DELOSH, DIRECTOR

LEGAL RESEARCH
STEVEN L. DALLE MURA, DIRECTOR

LEGISLATIVE & PUBLIC RELATIONS
KRISTI S. WRIGHT, DIRECTOR

MAGISTRATE SERVICES
MASON L. BYRD, DIRECTOR

October 1, 2016

The Honorable Thomas K. Norment, Jr.
Chairman of the Virginia State Crime Commission
Patrick Henry Building
1111 East Broad Street, Suite B036
Richmond, Virginia 23219

The Honorable William A. Hazel, Jr.
Secretary of Health and Human Resources
Patrick Henry Building
1111 East Broad Street
Richmond, VA 23219

The Honorable Emmett W. Hanger, Jr.
Chairman of the Senate Finance Committee
General Assembly Building
10th Floor
201 North 9th Street
Richmond, VA 23219

The Honorable Brian Moran
Secretary of Public Safety and Homeland Security
P.O. Box 1475
Richmond, VA 23218

The Honorable S. Chris Jones
Chairman of the House Appropriations Committee
Post Office Box 406
General Assembly Building
Richmond, Virginia 23218

The Honorable Daniel Timberlake
Director of the Department of Planning and Budget
1111 East Broad Street, Room 5040
Richmond, VA 23219

Re: Report Pursuant to Items 4 and 5, Paragraph H
2016-18 State Budget

Dear Gentlemen:

Item 4, Paragraph H, of the 2016 - 18 State Budget requires the Executive Secretary of the Supreme Court of Virginia to report the results of identified adult drug court sites for participation in a pilot program to provide substance abuse treatment utilizing non-narcotic, non-addictive, long acting, injectable prescription drug treatment regimens.

In addition, Item 5, Paragraph H requires the Executive Secretary of the Supreme Court of Virginia to report the results of two substance abuse treatment pilot programs at the Norfolk Adult Drug Court and the Henrico County Adult Drug Court utilizing non-narcotic, non-

addictive, long-acting, injectable prescription drug treatment regimens. Please find the enclosed specified report covering both budget items. If you have any questions about the report, please do not hesitate to contact me.

With best wishes, I am

Very truly yours,

Karl R. Hade

Enclosure

VIRGINIA DRUG TREATMENT COURTS: SUBSTANCE USE TREATMENT PILOTS

October 1, 2016

Office of the Executive Secretary

Supreme Court of Virginia

PREFACE

The Virginia 2016-2018 State Budget (Items 40 H. #4 and #5), *see* Appendix A, directs the Office of the Executive Secretary (OES) of the Supreme Court of Virginia to report the results of stakeholders review and of the pilot programs in Henrico and Norfolk, recommendations for expansion of the pilot program to other drug courts to the Secretaries of Public Safety and Homeland Security and Health and Human Resources, the Director of the Department of Planning and Budget, and the Chairmen of House Appropriations and Senate Finance Committees. This report reflects the first report due October 1, 2016.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The Virginia Governor's Task Force on Prescription Drug and Heroin Abuse was created to address the rising issue of prescription drug abuse as well as heroin use. The effects of such impacts every community across the Commonwealth and is an ever-growing problem. Medication-assisted treatments (MAT) have been proven to reduce relapse and rearrests. Vivitrol® has gained support to treat opioid use and alcohol use disorders. Results from pilot programs across the country show success using Vivitrol®. Participants have reported fewer side effects than with other treatments with both staff and participants reporting favoring over other medications. An Ohio study showed that six months following intake participant arrests for drug related offenses dropped from 80% to 50% (Baughman, M. & Singer, M., 2015).

The Task Force plan noted improvements were needed in access and availability to treatment service. Through the establishment of two pilot sites in the city of Norfolk and county of Henrico, access to less addictive treatments and to measure the outcomes would be provided. However, because of the varying coverage of Vivitrol® among Medicaid and private insurance providers, such access may not be completely possibly. Staff, healthcare providers and participants will need to be educated on coverage options for Vivitrol®. In other states, programs reported that although Vivitrol® had favorable outcomes, they were limited in what providers would provide thereby limiting options to receive treatment.

As the selected pilots, both adult drug treatment courts were requested to complete a grant application process in order to be approved, which included the following:

- A detailed description of the Vivitrol pilot program
- A copy of the Vivitrol Pilot Policy & Procedures Manual for their drug court program
- Compliance with the Medication-Assisted Treatment in Drug Courts Recommended Strategies, known as the Nine Components of Successful MAT Programs
- Compliance with the Medication Guide provided by Alkermes, the Vivitrol manufacturer

For these and future pilot programs to be successful; staff, participants, and providers will also need:

- Education
- Training
- Funding
- Access

While the medication-assisted treatment is reported as successful, it cannot be discounted that when coupled with other ancillary services the positive outcomes are even greater. States have recognized that many participants have co-occurring issues including mental health, housing, childcare, transportation, and unemployment. For treatment to truly work, a community wide effort is needed. The two pilots will seek to address the lack of access and funding that so many drug treatment court programs experience while also encouraging multi-disciplinary approaches. These pilots will also provide guidance and support for other future programs.

I. Introduction

As the opioid epidemic is ravaging communities across Virginia and the country, governments, communities, families, public health officials, and others are increasingly calling for all tools available to treat opioid addiction and save lives. For some individuals, prescription opioids are just the beginning. What begins as abuse, misuse, or overuse of a prescription opioid can evolve into the use of heroin, which is often less expensive and easier to obtain but has very similar effects. Prescription opioids, which are derived from some of the same sources as the street drug heroin, are used to treat both chronic and acute pain. They, like heroin, develop tolerance, can create dependence and overdosing which can cause death.

According to the 2011 Center for Disease Control report[1], nonmedical use of opioid pain relievers costs U.S. health insurers approximately $72.5 billion annually in healthcare costs. These include costs paid by Medicaid, a State-Federal insurance program that will increase in importance under the Affordable Care Act. In the Commonwealth, overdose deaths are occurring across all walks of life and in all parts of the state. The number of these fatalities is steadily rising. In fact, the number of deaths by overdose has risen to be greater than fatalities by car accidents or guns as tallied by the federal Centers for Disease Control and Prevention.

In November 2015, Governor McAuliffe created the Task Force on Prescription Drug and Heroin Abuse to address the growing and dangerous epidemic of prescription opioid and heroin abuse in Virginia. The overarching goal of the Task Force was focused on improving public safety and public health. As opioid overdoses increase and take the lives of more Virginians, the urgency that the Commonwealth faces compelled the Task Force to move forward with implementation of early proposals while continuing to refine other recommendations. A number of initiatives proposed by the Task Force were introduced as legislation in the 2015 session of the General Assembly. Several of these bills, (HB 1458, HB 1841, HB 1810, HB 1738, & HB 1747) which focused on the expanded availability of the overdose-reversing drug naloxone, and greater use of the Prescription Monitoring Program, were

[1] Health, United States, 2011

enacted into law. The Task Force also identified and began work on a number of initiatives that could be implemented without legislation.

The prescription drug and heroin overdose epidemic has been developing over the past several years. Combating a problem that is so complex in its causes, effects, and solutions will not be a swift or simple process. Preventing and ending these devastating overdose deaths among Virginians will require focus, dedication and coordination among all three branches of government, budget appropriations and possible statutory changes, and the engagement of state and local agencies, stakeholder groups, communities, families, and the public. Long-term solutions to this critical issue will require sustained interest and continuing investment.

As part of the Task Force's work, the treatment workgroup provided the following recommendation - Explore ways to enhance medication-assisted treatment (MAT) through CSBs, Drug Treatment Courts, and jail-based treatment. The Task Force further reported that "fewer than half of the CSBs currently utilize medication to assist treatment for individuals seeking recovery from opioid addiction. Barriers to providing MAT include limited funding, lack of access to a qualified physician or opiate treatment program, and lack of staff knowledge about how medication can assist recovery. Judges may also not be aware of the critical role that MAT can play in helping drug treatment court participants achieve success and instead insist on a "drug-free" model that is not supported by evidence. In addition, most drug treatment courts are not adequately funded to provide medication. Sheriffs and jail administrators also lack up-to-date information, access to qualified physicians and funding to support necessary staff and purchase medication." The treatment workgroup offered additional recommendations related to the lack of access to treatment for drug addiction in Virginia noting it as a major barrier to overcoming prescription opioid and heroin abuse, misuse and overuse.

Medications can interrupt the cycle of addiction to allow patients to increase their functioning, gain some control over their addiction, and engage in therapeutic recovery. Researchers, federal health agencies and pharmaceutical manufacturers have focused on developing medications that can be used to expand access to treatment for opioid use disorders. This has resulted in the Food and Drug Administration (FDA) approving medications for use in

treating alcohol and opioid use disorders. This treatment is called medication-assisted treatment (MAT). This paper will primarily focus on MAT using Naltrexone, in the extended-release injectable formulation, one of the three primary types of medications commonly prescribed to be used with MAT.

Medication-assisted treatment is the combination of medication, behavioral or cognitive-behavioral counseling, and other indicated psychosocial services, such as vocational or educational training (Center for Substance Abuse Treatment [CSAT], 2004, 2005). McLellan specifically identifies in his textbook that medication-assisted treatment draws attention to the role of medication as *assisting* other components of treatment (2008).

Beginning in 2015, drug courts receiving federal funding pursuant to the Adult Drug Court Discretionary Grant Program must attest in writing that they will not deny otherwise eligible candidates access to the program because of a candidate's use of an FDA-approved medication for the treatment of a substance use disorder, and they will not require participants to discontinue such medications as a condition of graduating from the program (U.S. Department of Justice, 2015). The grant language creates a difficult-to-rebut presumption that MAT will be permitted if it is prescribed lawfully by a licensed medical practitioner who has personally examined the participant, diagnosed him or her as having a substance use disorder, and determined that the medication is appropriate to treat the disorder. Drug courts may overrule such determinations only if the court finds that a participant has been misusing or abusing the medication or diverting the medication for unauthorized purposes. The MAT attestation applies only to drug courts receiving Bureau of Justice Assistance or Substance Abuse Mental Health Services Administration (SAMHSA) funding.

The National Drug Court Institute (NDCI) reports, that in a 2014 survey of all state and territorial drug court coordinators in the United States, opioids were ranked as the primary substance of abuse in approximately 20% of adult urban drug courts and in just over 30% of rural and suburban drug courts (Marlowe, Hardin, & Fox, 2016).

II. Naltrexone

The Substance Abuse and Mental Health Services Administration (SAMHSA) defines Naltrexone as "a medication approved by the FDA to treat opioid use disorders and alcohol use disorders. The injectable extended-release form of the drug (Vivitrol®) is administered at 380mg intramuscular once a month. Naltrexone can be prescribed by any health care provider who is licensed to prescribe medications. To reduce the risk of precipitated withdrawal, patients are warned to abstain from illegal opioids and opioid medication for a minimum of 7-10 days before starting Naltrexone." (Substance Abuse Mental Health Services Administration).

SAMHSA continues to warn that if a person relapses and uses the problem drug, Naltrexone prevents the feeling of getting high. Individuals using Naltrexone should not use any other opioids or illicit drugs; drink alcohol; or take sedatives, tranquilizers, or other drugs. Patients on Naltrexone may have reduced tolerance to opioids and may be unaware of their potential sensitivity to the same, or lower, doses of opioids that they used to take. If patients who are treated with Naltrexone relapse after a period of abstinence, it is possible that the dosage of opioid that was previously used may have life-threatening consequences, including respiratory arrest and circulatory collapse."

The National Institute on Drug Abuse (NIDA) describes Naltrexone as an opioid antagonist. Naltrexone is not addictive or sedating and does not result in physical dependence; however, poor patient compliance has limited its effectiveness. Recently an injectable long acting formulation of Naltrexone called Vivitrol® received FDA approval for treating opioid addiction. Given as a monthly injection, Vivitrol® is said to improve compliance by eliminating the need for daily dosing. To avoid withdrawal symptoms, Vivitrol® should be used only after a patient has undergone detoxification. Vivitrol® provides an effective alternative for individuals who are unable to or choose not to engage in medication-assisted treatment (NIDA, 2012).

A long-acting injectable formulation of Naltrexone with the brand name Vivitrol® was approved by the FDA in 2006 for alcohol dependence and in 2010 for the prevention of relapse of opioid dependence after detoxification. As a physician-prescribed clinician-administered injectable medication, it may be covered under a Medicaid plan's pharmacy benefit or medical

benefit unlike either the generic tablet form of Naltrexone or the various formulations of buprenorphine, which are almost always covered as outpatient pharmacy benefits. If listed under medical benefits as an injectable similar to certain cancer medications, the prescribing physician must first "buy and bill" the medication in order to be reimbursed by Medicaid or other health plans.

Unlike methadone or buprenorphine, Naltrexone is not a controlled substance; and since it is injected, there are no concerns about misuse or diversion. Furthermore, prescribers do not require any special training or certification, other than learning how to appropriately inject the medication in their offices. Another difference about Naltrexone is that it is a specialty pharmaceutical which must be administered by a health care provider. As it is not a self-administered specialty pharmaceutical, it is typically covered as a medical benefit with implications for the patient in terms of co-payments for office-based injection.

Abuse of opioids, especially heroin, is also linked with the transmission of human immunodeficiency virus (HIV), hepatitis, sexually transmitted infections (STIs), and other blood-borne diseases mostly through the use of unsterile drug paraphernalia, but also through the risky behavior that drug abuse may engender. Thus treatment of drug abuse not only frees individuals from the vicious cycle of addiction, but can also prevent related adverse health consequences.

Positive outcomes have also been reported for antagonist medications, such as Naltrexone, which are nonaddictive and nonintoxicating. Naltrexone blocks the effects of opiates and partially blocks the effects of alcohol without producing psychoactive effects of its own. Studies have reported significant reductions in heroin use and rearrest rates for opiate-addicted probationers and parolees who received Naltrexone (Cornish et al., 1997; Coviello et al., 2012; O'Brien & Cornish, 2006). In addition, at least two small-scale studies reported better outcomes in DWI Drug Courts or DWI probation programs for alcohol-dependent participants who received an injectable form of Naltrexone called Vivitrol® (Finigan et al., 2011; Lapham & McMillan, 2011).

III. Stakeholders

A stakeholders meeting is planned for late October 2016. Stakeholders invited include the Henrico County Drug Court team, the Norfolk Drug Court team, the Substance Use Disorder System of Care Policy Advisor of the Virginia Department of Behavioral Health and Developmental Services, Chief Deputy Commissioner at the Department of Health and the statewide Drug Court Coordinator.

The Vivitrol® pilot funds will be administered by the Office of the Executive Secretary to the two drug courts, Norfolk and Henrico Adult Treatment Courts, using a grant process. Each drug court must complete an application process that includes the following:

- A detailed description of the program
- A copy of the policy & procedures manual for the pilot
- Compliance with the Medication Guide provided by the Vivitrol® manufacturer

Note: As of the date of this report, the application process for the pilot programs is still underway and participants have not yet been enrolled.

The **Norfolk Adult Drug Treatment Court** intent is to use the funds to enhance their community services board's Opioid Treatment Program (OTP) using Vivitrol®. The program currently only offers Methadone. The OTP staff include professionals with medical, clinical and administrative expertise. Patients receive individually prescribed medication from a licensed medical practitioner and routinely meet with a primary counselor and attend clinic groups. Drug screens are used as a clinical tool to modify treatment approaches and interventions. Patients and their families receive education about substance addiction. Norfolk's program will use 90% of their funds in the 'supplies and other' category for the medication with the remaining balance in the 'consultant' budget category. The program estimates the cost of Vivitrol® at $1,000 per injection/dose.

The **Henrico Adult Drug Treatment Court** intends to issue a Request for Proposal (RFP) to contract for professional services with a prescriber. They will use 80% of their funds in the 'supplies and other' category for the medication with the remaining balance in the

'consultant' budget category. The program estimates the cost of Vivitrol® at the indigent price of $978 per injection/dose.

Virginia has attempted to address differing and increasing opioid addiction and related treatment issues with varying choices and levels of private insurance or Medicaid funding, if available, Substance Abuse Prevention and Treatment (SAPT) block grant funding, Prescription Monitoring Program (PMP), and other funding sources, including state and county revenues, child welfare funding, supportive housing funds, criminal justice, reentry and drug court funding and occasional correctional treatment funding.

Certain non-Medicaid funding sources that have been used previously, such as the Substance Abuse Prevention & Treatment (SAPT) block grant, may be reduced nationally as substance use disorder (SUD) funding for these opioid dependent patients is increasingly offered under Medicaid. The shift in SAPT block grant funding could be a particular problem for Virginia with no Medicaid expansion planned - or for those states whose Medicaid programs currently resist paying for one or all of the opioid medications. In Virginia, the non-Medicaid funding sources will likely continue to be even more critical to the opioid dependent patients, even if they access Medicaid funding for their medical care.

Dependence on opioid pain relievers, as well as addiction to heroin, is now widely recognized as a chronic disease, not a defect of character. As with other diseases, there are medications approved by the FDA through their science-based approval process as effective for treatment. There are currently three different FDA-approved medications, as well as several evidence-based counseling therapies used in Medication-Assisted Treatment – MAT, available to treat diagnosed opioid dependence. These could be available to and should be widely used by state Medicaid agencies for treatment of clinically appropriate patients in states and areas most affected by the epidemic in order to stem its death toll. However these medications must first be covered for and accessible to patients and prescribers under a state's Medicaid benefit rules in order for effective treatment, rather than avoidable overdose, relapse, morbidity and death, to take place for opioid-addicted Medicaid enrollees.

Despite varied state approaches to the implementation of the Affordable Care Act (ACA) and the expansion of Medicaid, many aspects of the ACA reforms have already been implemented through Federal regulation and statewide Medicaid waivers. These reforms often include substance use disorder benefits but may or may not include coverage of the three FDA approved opioid dependence medications. Given that many of the remaining provisions of the ACA, including the January 2014 launch of state and/or state-Federally administered health insurance exchanges, understanding the current status of Medicaid coverage for opioid pharmacotherapies and associated psychosocial therapies will be useful in developing future benefit policies.

In a 2013 report, *Advancing Access to Addiction Medications: Implications for Opioid Addiction Treatment* , at least forty-two (42) states, including Virginia, have some evidence collected through survey or secondary sources that they offer some Medicaid coverage of injectable sustained release Naltrexone (Vivitrol®), a more recently approved opioid dependence medication than buprenorphine/ naloxone or methadone. One state, South Dakota, indicated that Vivitrol® is not covered (The Avisa Group, 2013, pp. 25-26).

In general, the Medicaid agency information on injectable Naltrexone/ Vivitrol® was far less comprehensive than was the information on buprenorphine/ naloxone or on methadone. Likewise, a total of sixteen (16) states, including Virginia, were found to have imposed a counseling documentation requirement in order to approve administration of injectable Naltrexone, while another twenty-four (24) appear not to have such a requirement.

Only a small number of private insurance plans cover extended-release, injectable Naltrexone (Vivitrol®) and it is generally covered as both a medical and a pharmacy benefit with significant cost implications for patients. It is important to note that although evidence-based practice strongly suggests that clinical treatment, including counseling, should accompany use of medications, that requirement was rarely found in the survey health plans.

Some pre-authorization requirements make these funds more difficult to access where available. Training on what is and how it is covered under Medicaid is needed. No state covers

the medication and the counseling under the same category. Notable prior authorization requirements included: Vivitrol® Injectable Naltrexone (Vivitrol®) may be approved for the prevention of relapse to opioid dependence following detoxification when the individual:

- Is being treated for opioid dependence; and
- Has had an initial response and tolerates oral Naltrexone (Revia) but is unable to comply with daily dosing; and
- Has successfully completed an opioid detoxification program; and
- Has been opioid-free (including buprenorphine and methadone) for at least 7 days prior to initiating treatment with Naltrexone (Vivitrol®) injection; and
- Actively participates in a comprehensive rehabilitation program that includes psychosocial support; and
- Patient has none of the following:
  a. Currently on opioid analgesics for pain management; or
  b. Currently in acute opioid withdrawal; or
  c. A positive urine screen for opioids; or
  d. A failed naloxone challenge test; or
  e. Acute hepatitis; or
  f. Liver failure; or
  g. Previous hypersensitivity to Naltrexone, 75:25 polyactide-co-glycolide (PLG), carboxymethylcellulose or any other component of the diluent.

IV. Comparable Pilots in Other States

A. Kentucky

The administration of Vivitrol® or Naltrexone (the generic oral form of the drug) is not a requirement for drug court participants. A judge may refer a participant who is interested in Vivitrol® but prior to use they must be examined by a medical professional and Vivitrol® must be administered by a trained healthcare professional. Various insurance and Medicaid will cover Vivitrol® and the drug court will provide referrals for insurance assistance for participants who do not have coverage.

B. Ohio

Ohio implemented their Addiction Treatment Pilot Program (ATPP) in 2013. In their 2015 final report it was found that drug court staff and judicial officials have seen the ATPP program as beneficial and having a positive effect on their clients. Vivitrol® was reported as more beneficial to patients because it is a monthly injection as opposed to the

daily pill form of Naltrexone and more effectively reduces cravings (Ohio MHAS Addiction Treatment Pilot Program, 2015). The program observed that patients using Vivitrol® reported more mental clarity and fewer side effects compared to other drugs. Ohio is a Medicaid expansion state and patients are able to obtain Vivitrol® under both Medicaid FFS and MC plans. Patients also do not need to show proof of enrollment in a treatment program or history of substance abuse to be covered. Overall, drug courts and judicial officials reported medication-assisted treatment (MAT) programs as more favorable when coupled with other local agency services, to be truly effective it must be a multi-disciplinary approach.

C. Oklahoma

Oklahoma has proposed a House Bill HB2937 to support medication-assisted treatment for drug court participants as few drug courts allow it at the moment. This bill will allow individuals in drug court to voluntarily participate in the program given they are covered under Medicaid or by some other funding source whether it be a federal, state, private grant, or something else. The Department of Mental Health and Substance Abuse Services would promote and implement the program and, if passed, would become effective November 1, 2016. As of this report, the bill has passed the House and is pending in the Senate.

D. Pennsylvania

Pennsylvania began county recruitment June 2016 for their Non-Narcotic Medication Assisted Treatment (MAT) Pilot Program. The program is being established by the Pennsylvania Department of Corrections (PA DOC) to increase opportunities for counties to provide long acting non-narcotic, non-addictive medication (Vivitrol®: Naltrexone for extended-release injectable suspension, 380 mg/vial) combined with comprehensive substance abuse treatment to eligible offenders upon release from county correctional institutions. Reports indicate the state has chosen Vivitrol® as it provides long-acting, non-addictive medication treatment. A requirement of this program is that Medicaid managed care plans must approved the medication through the prior authorization

process and Medicaid must also approve it for eligible offenders who are in the pilot program.

V. Recommendation

The following recommendation made here support the Governor's Prescription Drug and Heroin Task Force Implementation Plan Recommendation to explore ways to enhance MAT through community services boards, drug treatment courts, and jail-based treatment and the implementation steps to enhancing MAT.

Explore ways to enhance Medication-assisted Treatment (MAT) through CSBs, Drug Treatment Courts, and jail-based treatment.

Fewer than half of the Community Services Boards (CSBs) currently utilize medication to assist treatment for individuals seeking recovery from opioid addiction. Barriers to providing MAT include limited funding, lack of access to a qualified physician or opiate treatment program, and lack of staff knowledge about how medication can assist recovery. Judges and their drug court teams may benefit from education regarding the critical role that MAT can play in helping drug treatment court participants achieve recovery. Additional funding would be needed as most Drug Treatment Courts are not adequately funded, and do not have funds to provide medication. Sheriffs and jail administrators could benefit from up-to-date information, access to qualified physicians, and funding to support necessary staff and to purchase medication.

To implement this recommendation, the following steps should be taken -

- Virginia Department of Behavioral Health & Developmental Services (DBHDS) collaborates with the Substance Abuse Council of the Virginia Association of Community Services Boards (CSBs) to develop and provide training and technical assistance to CSB staff and contract agencies about evidence-based methods of treating opioid addiction and successful methods of implementing MAT in their treatment systems. Necessary resources and infrastructure will be identified.
- DBHDS collaborates with the Office of the Executive Secretary, Supreme Court of Virginia Drug and its Statewide Drug Court Advisory committee, and the Virginia

Association of Drug Treatment Courts (VADTC) to develop information, training and technical assistance to improve the use of MAT in drug treatment courts.

- DBHDS collaborates with the Substance Abuse Council of the Virginia Association of Community Services Boards, the Virginia Sheriffs' Association and the Department of Criminal Justice Services (DCJS) to explore methods of increasing access to medication-assisted treatment for individuals incarcerated in local jails.

The extended-release form of Naltrexone has only been FDA-approved since 2010 and research on results is limited. There is some evidence that the extended-release form may partially ameliorate the problem of prescription persistence that affects the oral version and improve compliance with Naltrexone therapy, as the medication remains active for 30 days with a single injection (Baser et al., 2011). However, recent studies of opiate-addicted adults have found poor to modest compliance to treatment with extended-release Naltrexone (Everly et al., 2011; DeFulio et al., 2012), though treatment compliance was substantially higher when employment-based reinforcement incentives were made contingent on treatment. Compliance with treatment using extended-release Naltrexone was much higher among opioid-dependent patients in a 24-week study conducted in Russia, where methadone and buprenorphine are not approved and where family members were recruited to help ensure compliance to therapy (Krupitsky et al., 2011).

Both the oral and extended-release formulations of Naltrexone have been associated with patient deaths due to accidental overdoses of opioids while taking one or other of the medications (Deguisto, Shakeshaft, Ritter, O'Brien, & Mattick, 2004). In many cases, overdosing may be due to the blocking effect of Naltrexone, with relapsing patients taking large amounts of opioids to try to overcome the blockage (Substance Abuse and Mental Health Services Administration, 2009; Kleber, 2007). In addition, patients treated with extended-release Naltrexone may have reduced tolerance to opioids and be unaware of their potential sensitivity to the same, or lower, doses that they used to take of opioids. For such patients who relapse after a period of abstinence, the dosages of opioids previously used may have life-threatening consequences, including respiratory arrest and circulatory collapse (Alkermes, Inc., 2013;

Substance Abuse and Mental Health Services Administration, 2013). Patients undergoing Naltrexone therapy should be clearly cautioned about these dangers.

Injection site reactions have been reported for extended-release Naltrexone. Treatment guidelines emphasize that extended-release Naltrexone must be injected only intramuscularly and never intravenously, subcutaneously, or into fatty tissues, using the kit included with the medication (Substance Abuse and Mental Health Services Administration, 2013).

The side effects of Naltrexone itself are generally mild. The medication can result in anxiety, nervousness, sleep problems, tiredness, joint or muscle pain, and headaches in some patients. Some additional side effects of extended-release naltrexone have been reported including nausea, vomiting, headache, fatigue, and muscle cramps.

Contraindications of Naltrexone include physiological dependence on opioids. Those currently physiologically dependent on opioids should be offered detoxification treatment or be referred to specialist services. Patients must have been fully withdrawn from all opioids before considering therapy with Naltrexone. Other contraindications include acute hepatitis or liver\ failure, as Naltrexone can be hepatotoxic in high doses. In view of its hepatotoxic effects, its use in patients with active liver disease must be carefully considered, with doses causing hepatic injury being at most fivefold of those that appear to be safe (TIP 49). Use of Naltrexone for treatment of chronic pain requires specialist assessment (Bell et al., 2003) and is contraindicated in patients with a history of sensitivity to the medication, to structurally similar compounds such as naloxone or nalmefene, or to any inactive ingredients in the tablet. Naltrexone should be used with careful monitoring of patients with moderate to severe renal impairment as the medication and its active metabolite are excreted through the urine
(SAMHSA, TIP 49).

Naltrexone in both the oral and extended-release formulations has been shown to have various interactions with other medications. Lethargy and somnolence have been reported when Naltrexone is used with chlorpromazine (Thorazine®) or thioridazine (Mellaril®), and caution should be taken when Naltrexone is used with antipsychotic drugs. Patients who are taking

yohimbine (Aphrodyne, Yocon) at the same time may experience anxiety, increased pulse, and elevated blood pressure (SAMHSA, Center for Substance Abuse Treatment, 2009). Patients taking Naltrexone experience significant blockade of opioid effects from medications taken for analgesia. This blockade is present only when Naltrexone is taken regularly and will cease 24 to 72 hours after the medication is discontinued (O'Connor & Fiellin, 2000). Cough/cold and antidiarrheal medications containing opioids may decrease the benefit of Naltrexone, and patients may require a greater amount of opioid analgesics than usual, possibly resulting in deeper and more prolonged respiratory depression (Bell et al., 2003).

While there are no clear recommended guidelines for the duration of Naltrexone therapy, 6 to 12 months is probably a minimum in most cases. Naltrexone can be stopped abruptly without withdrawal symptoms, but before discontinuing this medication, a careful clinical evaluation of the risk for relapse should be conducted (Kleber, 2007).

Funds for medication-assisted treatment options should be made available to the treatment providers serving drug courts. It is the role of a competent, properly licensed physician to determine, based on the best available information, what regimen is most likely to be successful for a given patient. It is also the responsibility of a physician to explain this decision-making process to nonmedical persons, including the patient, the patient's loved ones, and third-party payers. Duly trained treatment professionals provide the counseling and other treatment services correlating with the medical treatment. Failing to consider scientific evidence when making decisions about MAT falls short of best practice standards (NADCP, 2013, 2015) and may under some circumstances amount to an abuse of judicial discretion.

Appendix A

Virginia 2016-2018 State Budget (Items 40 H. #4 and #5):

4. The Executive Secretary of the Supreme Court of Virginia shall identify eligible adult drug court sites for participation in a pilot program to provide substance abuse treatment utilizing non-narcotic, non-addictive, long acting, injectable prescription drug treatment regimens. The Executive Secretary shall identify the state funding resources necessary to support pilot program medication, provider fees, counseling, and patient monitoring, as well as any available local or regional funding resources available. The Executive Secretary shall meet with and solicit feedback from stakeholders including requesting information on the success of comparable pilot programs in other states. The Executive Secretary shall report the results of this review, as well as recommendations for establishment of the pilot program to other drug courts, to the Secretaries of Public Safety and Homeland Security and Health and Human Resources, the Director of the Department of Planning and Budget, and the Chairmen of the House Appropriations and Senate Finance Committees by October 1, 2016. All Adult Drug Courts in the Commonwealth shall provide all necessary information to the Office of the Executive Secretary of the Supreme Court of Virginia in order to conduct such a review.

5. Included in this item is $100,000 the first year and $100,000 the second year from the general fund to support two substance abuse treatment pilot programs at the Norfolk Adult Drug Court and the Henrico County Adult Drug Court utilizing non-narcotic, non-addictive, long-acting, injectable prescription drug treatment regimens. The Norfolk and Henrico County Adult Drug Courts shall utilize these resources to support pilot program medication, provider fees, counseling, and patient monitoring. The Executive Secretary of the Supreme Court shall report the results of the pilot program, as well as recommendations for expansion of the pilot program to other drug courts, to the Secretaries of Public Safety and Homeland Security and Health and Human Resources, the Director of the Department of Planning and Budget, the Chairman of the Virginia State Crime Commission, and the Chairmen of the House Appropriations and Senate Finance Committees by October 1 each year of the pilot program. The Norfolk and Henrico County Adult Drug Courts shall provide all necessary information to the Office of the Executive Secretary to conduct such an evaluation.

Appendix B

For additional specific information for the non-narcotic, non-addictive, long acting, injectable prescription drug please consult the following brief guide made available through SAMHSA.

Clinical Use of Extended-Release Injectable Naltrexone in the Treatment of Opioid Use Disorder: A Brief Guide
http://store.samhsa.gov/product/Clinical-Use-of-Extended-Release-Injectable-Naltrexone-in-theTreatment-of-Opioid-Use-Disorder-A-Brief-Guide/SMA14-4892R

References

Alkermes, Inc. Medication guide. Revised November 2010, VIV993B). Waltham, MA: Alkermes, 2013. [Accessed at http://www.vivitrol.com/Content/pdf/medication_guide.pdf

American Society of Addiction Medicine. (2013, June). Availability without Accessibility? State Medicaid Coverage and Authorization Requirements For Opioid Dependence Medications. Retrieved from: aaam_implications-for-opioid-addiction-treatment_final.pdf

Baser, O., Chalk, M., Fiellin, D. A., & Gastfriend, D. R. (2011). Cost and utilization outcomes of opioid dependence treatments. *The American Journal of Managed Care*, *17*(8), S235-S248.

Bell, J., Kimber, J., Lintzeris, N., White, J., Monheit, B., Henry-Edwards, S., . . . Quigley, A. (2003).*Clinical guidelines and procedures for the use of naltrexone in the management of opioid dependence*. Publications Production Unit, Australian Government Department of Health and Ageing.

Baughman, M. & Singer, M. (2015). *2015 Annual Report of the Ohio MHAS Addiction Treatment.* Retrieved from *http://mha.ohio.gov/Portals/0/assets/Initiatives/ATPP/2015-ATP-Begun-Center-Final-Report.pdf*

Centers for Disease Control and Prevention (CDC). (2011, November 4). Vital sign: Overdoses of prescription opioid pain relievers—United States, 1999-2008. MMWR. Morbidity and Mortality Weekly Reports. Retrieved from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5912a2.htm

Center for Substance Abuse Treatment. (2009). Incorporating Alcohol Pharmacotherapies Into Medical Practice. Rockville (MD): Substance Abuse and Mental Health Services Administration (US). (Treatment Improvement Protocol (TIP) Series, No. 49.) Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK64041/

Center for Substance Abuse Treatment. (2005). Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Rockville (MD): Substance Abuse and Mental Health Services Administration (US). (Treatment Improvement Protocol (TIP) Series, No. 43.) Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK64164/

Comer, S.D., Sullivan, M.A., Yu, E., et al. (2006). Injectable, sustained-release naltrexone for the treatment of opioid dependence. *Archives of General Psychiatry*, *63*, 210–218.

Cornish, J.W., Metzger, D., Woody, G.E., Wilson, D., McLellan, A.T., Vandergrift, B., & O'Brien, C.P. (1997). Naltrexone pharmacotherapy for opioid dependent federal probationers. Journal of Substance Abuse Treatment, 14(6), 529–534.

DeFulio, A. & Silverman, K. The use of incentives to reinforce medication adherence. *Preventive Medicine*, 55(Suppl 1), S86-S94.

Degiusto, E., Shakeshaft, A., Ritter, A., O'Brien, S., & Mattic, R. P. Serious adverse events in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD). *Addiction, 99*(4), 450-460.

Everly, J. J., DeFulio, A., Koffarnus, M. N., Leoutsakos, J. M. S., Donlin, W. D., Aklin, W. M., Silverman, K. (2011). Employment-based reinforcement of adherence to depot naltrexone in unemployed opioid-dependent adults: A randomized controlled trial. *Addiction, 106*(7), 1309-1318.

Finigan, M.W., Perkins, T., Zold-Kilbourn, P., Parks, J., & Stringer, M. (2011). Preliminary evaluation of extendedrelease naltrexone in Michigan and Missouri drug courts. Journal of Substance Abuse Treatment, 41(3), 288–293.

Kleber, H. D. (2007). Pharmacologic treatments for opioid dependence: detoxification and maintenance options. [Review]. *Dialogues in Clinical Neuroscience, 9*(4), 455-470.

Krupitsky, E., Nunes, E. V., Ling, W., Illeperuma, A., Gastfriend, D. R., & Silverman, B. L. (2011). Injectable extended-release naltrexone for opioid dependence: A double-blind, placebo-controlled, multicentre randomised trial. *The Lancet, 377*(9776), 1506-1513

Lapham, S.C., & McMillan, G.P. (2011). Open-label pilot study of extended-release naltrexone to reduce drinking and driving among repeat offenders. Journal of Addiction Medicine, 5(3), 163–169.

Legal Action Center. (2009). Know your rights: Rights for individuals on medication-assisted treatment (HHS Publication No. [SMA] 09-4449]. Rockville, MD: Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration.

Marlowe, D.B., Hardin, C.D., & Fox, C.L. (2016). Painting the current picture: A national report on drug courts and other problem solving courts in the United States. Alexandria, VA: National Drug Court Institute.

McLellan, A.T., Lewis, D.C., O'Brien, C.P., & Kleber, H.D. (2000). Drug dependence, a chronic medical illness: Implications for treatment, insurance, and outcomes evaluation. JAMA, 284(13), 1689-1695.National Institute on Drug Abuse (NIDA). (2013). Drug facts: Heroin. Retrieved from: http://www.drugabuse.gov/publications/drugfacts/heroin

National Association of Drug Court Professionals. (2013). Adult Drug Court best practice standards (Vol. I). Alexandria, VA: Author. Retrieved from http://www.nadcp.org/sites/default/files/nadcp/AdultDrugCourtBestPracticeStandards.pdf

National Association of Drug Court Professionals. (2015). Adult Drug Court best practice standards (Vol. II). Alexandria, VA: Author. Retrieved from http://www.ndcrc.org/sites/default/files/adult_drug_court_best_practice_standards_volume_ii.pdf

O'Brien, C., & Cornish, J.W. (2006). Naltrexone for probationers and parolees. Journal of Substance Abuse Treatment, 31(2), 107–111.

O'Connor, P. G., & Fiellin, D. A. (2000). Pharmacologic treatment of heroin-dependent patients. *Annals of Internal Medicine, 133*(1), 40-54

Pennsylvania General Assembly. SB 524. Regular Session 2015-2016. December 17, 2015.An Act amending Title 61 (Prisons and Parole) of the Pennsylvania Consolidated Statutes, establishing the Non-narcotic Medication Assisted Substance Abuse Treatment Grant Pilot Program; and, imposing powers and duties on the Department of Corrections.

SAMHSA, Center for Substance Abuse Treatment, 2009, *Incorporating alcohol pharmacotherapies Into medical practice (TIP 49*).

Oklahoma State Legislature. 2nd Session of the 55th Legislature (2016). HB 2937. February 1, 2016. Drug courts; authorizing Department of Mental Health and Substance Abuse Services to implement a pilot program for certain drug court participants; effective date.

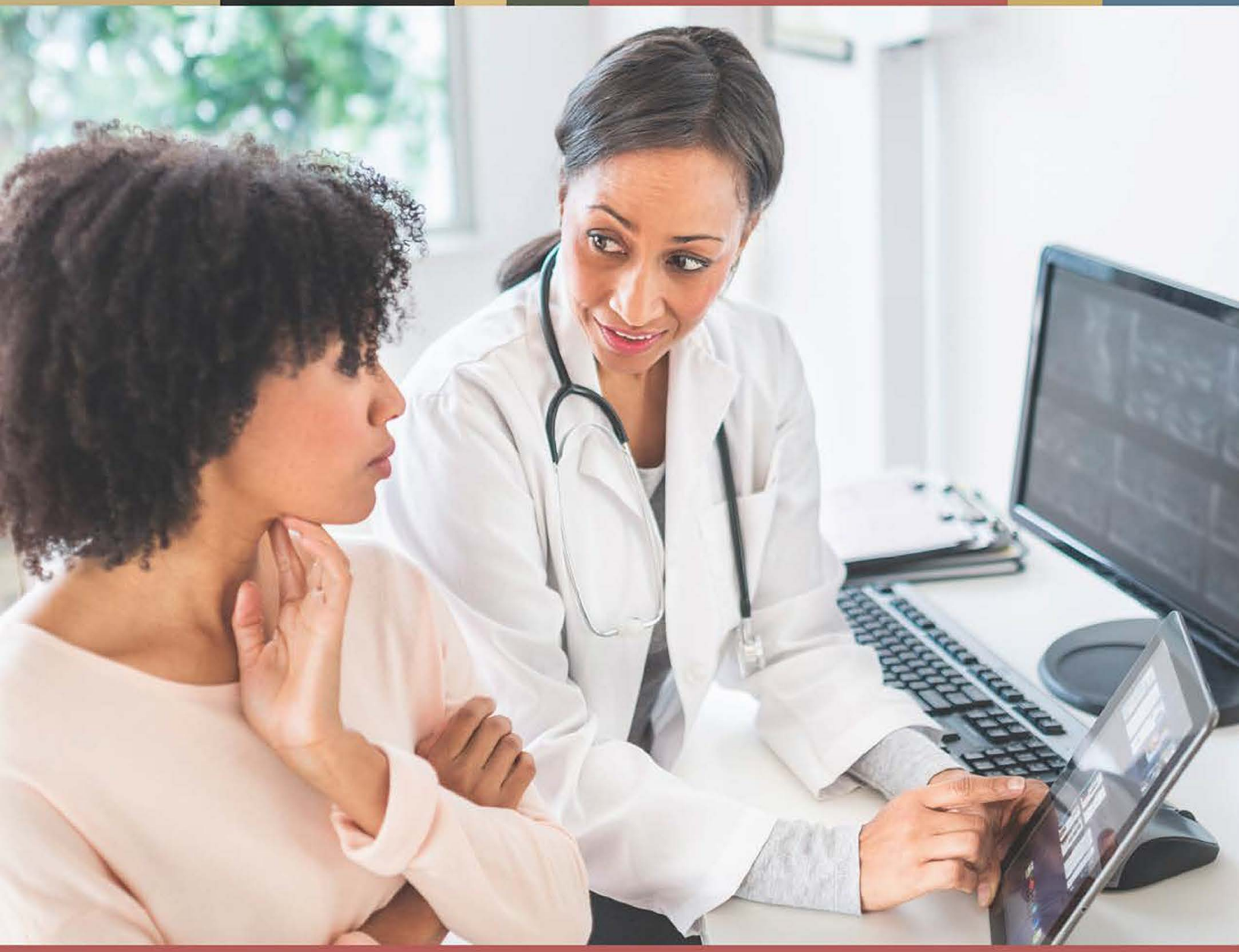
Substance Abuse and Mental Health Services Administration (SAMHSA). (2011). Medication-Assisted Treatment for Opioid Addiction: 2010 State Profiles (HHS Publication No. SMA-11-4643). Rockville, MD: Substance Abuse and Mental Health Services Administration.

Substance Abuse and Mental Health Services Administration. (2012). An introduction to extended release injectable naltrexone for the treatment of people with opioid dependence. SAMHSA Advisory, 11(1), 1–8. Retrieved from http://store.samhsa.gov/shin/content/SMA12-4682/SMA12-4682.pdf

Substance Abuse and Mental Health Services Administration. (2014). National Survey of Substance Abuse Treatment Services (N-SSATS): 2013: Data on substance abuse treatment facilities (BHSIS Series S-73, HHS Publication No. [SMA] 14-489). Rockville, MD: Author. Retrieved from http://www.samhsa.gov/data/%20sites/default/files/2013_N-SSATS/2013_N-%20SSATS_National_Survey_of_Substance_Abuse_Treatment_%20Services.pdf

U.S. Department of Justice, Office of Justice Programs, Bureau of Justice Assistance. (2015). Adult Drug Court Discretionary Grant Program FY 2015 Competitive Grant Announcement (OMB No. 1121-0329). Retrieved from https://www.bja.gov/Funding/15DrugCourtSol.pdf

Clinical Use of Extended-Release Injectable Naltrexone in the Treatment of Opioid Use Disorder: A Brief Guide



Substance Abuse and Mental Health Services Administration
SAMHSA
www.samhsa.gov • 1-877-SAMHSA-7 (1-877-726-4727)

Clinical Use of Extended-Release Injectable Naltrexone in the Treatment of Opioid Use Disorder:
A Brief Guide

Revised February 2, 2015

U.S. Department of Health and Human Services
Substance Abuse and Mental Health Services Administration
Center for Substance Abuse Treatment
Division of Pharmacologic Therapies

1 Choke Cherry Road
Rockville, MD 20857

Acknowledgments

This report was prepared for the Substance Abuse and Mental Health Services Administration (SAMHSA) by JBS International, Inc. under contract number HHSS283200700003I/HHSS28342007T, with SAMHSA, U.S. Department of Health and Human Services (HHS). CDR Alina Salvatore, R.Ph., M.S., and LCDR Brandon T. Johnson, M.B.A., served as the Contract Officer's Representative.

Disclaimer

The views, opinions, and content expressed herein are the views of the authors and do not necessarily reflect the official position of SAMHSA or HHS. Nothing in this document constitutes an indirect or direct endorsement by SAMHSA or HHS of any non-federal entity's products, services, or policies and any reference to a non-federal entity's products, services, or policies should not be construed as such. No official support of or endorsement by SAMHSA or HHS for the opinions, resources, and medications described is intended to be or should be inferred. The information presented here in this document should not be considered medical advice and is not a substitute for individualized patient or client care and treatment decisions.

Electronic Access and Printed Copies

This publication may be downloaded or ordered at **http://store.samhsa.gov.** Or call SAMHSA at 1-877-SAMHSA-7 (1-877-726-4727) (English and Español).

Recommended Citation

Substance Abuse and Mental Health Services Administration*. Clinical Use of Extended-Release Injectable Naltrexone in the Treatment of Opioid Use Disorder: A Brief Guide.* HHS Publication No. (SMA) 14-4892R. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2015.

Originating Office

Division of Pharmacologic Therapies, Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, 1 Choke Cherry Road, Rockville, MD 20857. HHS Publication No. (SMA) 14-4892R. Printed 2015.

CONTENTS

INTRODUCTION

The profile of opioid misuse and opioid use disorder in the United States is changing, in that nonmedical use of prescription opioids has become as significant a problem as the use of heroin.[1] Federal data for 2013 indicate that approximately 4.5 million people in the United States reported nonmedical use of prescription pain relievers in the past month and 289,000 reported use of heroin in the past month.[2] Despite the dimensions of the problem, nearly 80 percent of people with an opioid use disorder do not receive treatment because of limited treatment capacity, financial obstacles, social bias, and other barriers to care.[3]

A diagnosis of opioid use disorder continues to carry significant social bias, which affects both the individuals who receive the diagnosis and the health care professionals to whom such individuals may turn for care.

Researchers, federal health agencies, and pharmaceutical manufacturers have focused on developing medications that can be used to expand access to treatment of an opioid use disorder in medical office settings, rather than limiting use to specialized opioid treatment programs (OTPs).[4] This effort has yielded two important products that the Food and Drug Administration (FDA) has approved for use in treating an opioid use disorder and/or preventing relapse: buprenorphine (alone and in combination with naloxone) and naltrexone (in an oral formulation and an extended-release injectable formulation). These medications differ in mechanism of action, route and frequency of administration, and certain regulatory restrictions on their use as shown in Table 1 on page 4.

After reviewing multiple studies, many experts in addiction have concluded that patients who have an opioid use disorder should be offered medication-assisted treatments on a routine basis.[5] However, considerable resistance to the use of such treatments persists. A diagnosis of opioid use disorder continues to carry significant social bias, which affects both the individuals who receive the diagnosis and the health care professionals to whom such individuals may turn for care.[*6]

With practical resources, the unmet need for treatment and the largely untapped resource of primary care medicine can be brought together to yield healthier patients who are treated in safer environments and an expanded repertoire of effective professional practices for primary care providers. In fact, many studies show that the treatment of an opioid use disorder can be successfully integrated into general office practice by physicians and health providers who are not addiction specialists.[7–15]

To review the options available for the treatment of opioid use disorder, the Substance Abuse and Mental Health Services Administration (SAMHSA) and the National Institute on Drug Abuse (NIDA) jointly convened the Consensus Panel on New Pharmacotherapies for Opioid Use Disorders and Related Comorbidities (see Appendix A). Composed of experts in research, clinical care, medical education, and public policy, the panel reviewed current evidence on the effectiveness of available medications for the treatment of an opioid use disorder and developed a guidance for clinical practice.[5] The panel's guidance is presented in this document.

[*] The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; American Psychiatric Association, 2013)[6] uses the term *opioid use disorder* to include abuse of or dependence on opioids. The specific indication for which extended-release injectable naltrexone was approved by FDA is prevention of relapse to opioid dependence, following opioid detoxification, which is subsumed by the DSM-5 term *opioid use disorder*.

ASSESSING THE NEED FOR TREATMENT

Patient Assessment

A patient who is identified with a potential opioid use disorder should undergo a thorough assessment to confirm the diagnosis.[16] The objectives of the assessment are to determine the patient's need for treatment, to develop a treatment plan, and to establish a baseline measure for evaluating the patient's progress. Accordingly, the patient assessment should:

- Confirm the opioid use disorder diagnosis
- Establish current opioid use—when, what, and how much opioid the patient used most recently
- Document the patient's substance use history, including alcohol and other drugs of abuse
- Identify patients who require medically supervised detoxification from alcohol, benzodiazepines, or other sedatives, in addition to opioids
- Determine where and when such detoxification should be accomplished
- Identify comorbid medical and psychiatric conditions and disorders and prioritize and coordinate their management
- Screen for infectious diseases for which people who misuse opioids are at elevated risk, such as hepatitis B , hepatitis C and HIV/AIDS
- Assess the patient's access to social supports, family, friends, employment, housing, finances, and assistance with legal problems
- Evaluate the patient's degree of motivation for behavior change and readiness to participate in treatment

The physical examination should focus on problems the patient is experiencing and include screening for common consequences or co-occurring problems associated with the patient's current and past substance use.

Substance Use History. A complete substance use history is essential to development of a safe and appropriate treatment plan.[17] In-depth interviews, combined with the use of standardized assessment instruments, are effective methods of gathering this information. Ideally, the substance use history should include the nature of the patient's substance use disorders, underlying or co-occurring diseases or conditions, the effect of opioid use on the patient's physical and psychological functioning, and the outcomes of past treatment episodes.

It is essential to find out whether the patient is currently taking (or recently took) methadone or other long-acting opioids.[18,19] Urine toxicology screens must also be completed. It also is advisable to access the patient's prescription drug use history through the state's prescription drug monitoring program (PDMP)[20] where available, both to confirm compliance in taking prescribed medications and to detect unreported use of other prescription medications.[17] Information about PDMPs and how to access them is available from state boards of medicine and pharmacy.

Information about PDMPs and how to access them is available from state boards of medicine and pharmacy.

In addition to securing the patient's PDMP record, obtaining information from family members and significant others can provide useful perspectives on the patient's behavior and level of function, so consent to speak with family members and other providers must be obtained. Contact with or records from clinicians who have treated the patient in the past and information from the prescription benefit provider should also be sought out.[10]

Physical Examination. The physical examination of a patient who is being evaluated for a substance use disorder should focus on physical findings related to addiction and its complications. For example, examination of skin injection sites can provide useful information about the duration of injection drug use. Recent injection marks are small and red and sometimes are inflamed or surrounded by slight bruising. Older injection sites typically are not inflamed but sometimes show pigmentation changes (either lighter or darker), and the skin may have an atrophied or sunken appearance. A combination of recent and old injection sites suggests that the

patient may be currently using opioids and may have a complex opioid use disorder.[21]

The physical examination should address body systems related to reported symptoms. In asymptomatic people, height, weight, and blood pressure should be recorded, and a cardiac examination (listening for murmurs or cardiac rhythm abnormalities) should be performed.[22]

Laboratory Tests. A urine drug screen or other toxicology screen should be part of the patient assessment to confirm recent opioid use and to screen for use of other drugs. A urine test for alcohol (ethyl glucuronide) also needs to be included. Ideally, a drug screen should test for all opioids commonly prescribed and/or misused in the local community, as well as illicit drugs that are available locally.[23]

Other useful tests include those of liver enzymes and serum bilirubin, as well as tests for hepatitis B and C and HIV, particularly in patients who have engaged in injection drug use. For those patients who inject drugs, serum creatinine levels should be tested for the presence of silent renal disease.[22]

Developing a Treatment Plan

Treatment of an opioid use disorder should be guided by an individualized plan that is developed in consultation with the patient.[24] Elements of such a plan include the following:

- The role of medications in the patient's treatment and the rationale for their selection
- Referral and follow-up plans for specialty addiction treatment, psychosocial treatment, and/or family therapy, if clinically indicated
- Motivation for participating in mutual-help groups
- A discussion of the involvement of family or significant others in treatment
- A plan for treating co-occurring medical or psychiatric disorders
- Schedules for follow-up office visits and laboratory testing to monitor the patient's progress and health status
- Criteria for discontinuing use of the medication

The plan should be written to measure progress during the monitoring process.[22,25] The plan and the steps taken to implement it should be documented in the patient's medical record.[17]

Use of Medications. Whenever a medication is to be used, the treatment plan should give attention to steps that will promote medication adherence.[26] Depending on the needs of the patient, these steps might include specific strategies for remembering to take medications, use of blister-card packs or pill boxes, a schedule for monitoring medication adherence that reflects the patient's history of adherence to other medication regimens, and steps to involve the patient's family members in monitoring adherence.

Naltrexone functions as an opioid antagonist, whereas methadone is an opioid agonist and buprenorphine is an opioid partial agonist. Patients should abstain from using any opioids, including opioid-containing medicines, for a minimum of 7 to 10 days before starting extended-release injectable naltrexone to avoid precipitation of opioid withdrawal. Patients transitioning from buprenorphine or methadone may be vulnerable to precipitation of withdrawal symptoms for as long as 2 weeks.[26,27]

All medications for the treatment of the opioid use disorder should be prescribed as part of a comprehensive treatment approach that includes counseling and other psychosocial therapies delivered by a psychiatrist, psychologist, or professional counselor, as well as social support through participation in Narcotics Anonymous (NA) and other mutual-help programs.[1,5] Health care providers who choose to offer medication-assisted treatment in their office practices need to understand the nature of the underlying disorder, the specific actions of each available medication (and the associated contraindications or cautions), and the importance of careful patient selection and monitoring.[8]

Table 1 summarizes key information about three medications currently approved to treat opioid use disorders (extended-release injectable naltrexone, methadone, and buprenorphine). Only one column in the table is devoted to naltrexone because the prescribing considerations for extended-release injectable naltrexone and oral naltrexone are similar.[26]

TABLE 1: KEY FEATURES OF MEDICATIONS APPROVED FOR TREATING OPIOID USE DISORDER*

Prescribing Considerations	Extended-Release Injectable Naltrexone	Methadone	Buprenorphine
Frequency of Administration	Monthly†	Daily	Daily (also alternative dosing regimens)
Route of Administration	Intramuscular (IM) injection into the gluteal muscle by a physician or other health care professional.†	Orally as liquid concentrate, tablet or oral solution of diskette or powder.	Oral tablet or film is dissolved under the tongue.
Who May Prescribe or Dispense	Any individual who is licensed to prescribe medicines (e.g., physician, physician assistant, nurse practitioner) may prescribe and/or order administration by qualified staff.	SAMHSA-certified OTPs dispense methadone for daily administration either on site or, for stable patients, at home.	Physicians must have board certification in addiction medicine or addiction psychiatry and/or complete special training to qualify for the federal waiver to prescribe buprenorphine, but any pharmacy can fill the prescription. There are no special requirements for staff members who dispense buprenorphine under the supervision of a waivered physician.
Pharmacologic Category	Opioid antagonist	Opioid agonist	Opioid partial agonist Buprenorphine's partial agonist effect relieves withdrawal symptoms resulting from cessation of opioids. This same property will induce a syndrome of acute withdrawal in the presence of long-acting opioids or sufficient amounts of receptor-bound full agonists. Naloxone, an opioid antagonist, is sometimes added to buprenorphine to make the product less likely to be abused by injection.

* Table 1 highlights some properties of each medication. It does not provide complete information and is not intended as a substitute for the package inserts or other drug reference sources used by clinicians (see http://www.dailymed.nlm.nih.gov for current package inserts). For patient information about these and other drugs, visit the National Library of Medicine's MedlinePlus (http://www.medlineplus.gov). Whether a medication should be prescribed and in what amount are matters to be discussed between an individual and his or her health care provider. The prescribing information provided here is not a substitute for the clinician's judgment, and the National Institutes of Health and SAMHSA accept no liability or responsibility for use of the information in the care of individual patients.

† Naltrexone hydrochloride tablets (50 mg each) are also available for daily dosing.

Prescribing Considerations	Extended-Release Injectable Naltrexone	Methadone	Buprenorphine
Clinical Uses/Ideal Candidates	Prevention of relapse to opioid use disorder following opioid detoxification; studies suggest benefits for patients who are experiencing increased stress or other relapse risks (e.g., visiting places of previous drug use, loss of spouse, loss of job). Appropriate for patients who have been detoxified from opioids and who are being treated for a co-occurring alcohol use disorder. Extended-release naltrexone should be part of a comprehensive management program that includes psychosocial support. Other good candidates include persons with a short or less severe addiction history or who must demonstrate to professional licensing boards or criminal justice officials that their risk of opioid use is low.	Detoxification and maintenance treatment of opioid addiction. Patients who are motivated to adhere to the treatment plan and who have no contraindications to methadone therapy. Methadone should be part of a comprehensive management program that includes psychosocial support.	Treatment of opioid dependence. Patients who are motivated to adhere to the treatment plan and who have no contraindications to buprenorphine therapy. Buprenorphine should be part of a comprehensive management program that includes psychosocial support.
Contraindications	Contraindicated in patients receiving long-term opioid therapy. Contraindicated in patients who are engaged in current opioid use (as indicated by self-report or a positive urine drug screen) or who are on buprenorphine or methadone maintenance therapy, as well as in those currently undergoing opioid withdrawal. Contraindicated in patients with a history of sensitivity to polylactide-co-glycolide, carboxymethylcellulose, or any components of the diluent. Should not be given to patients whose body mass precludes IM injection with the 2-inch needle provided; inadvertent subcutaneous injection may cause a severe injection site reaction. Should not be given to anyone allergic to naltrexone.	Contraindicated in patients who are hypersensitive to methadone hydrochloride or any other ingredient in methadone hydrochloride tablets, diskettes, powder or liquid concentrate. Contraindicated in patients with respiratory depression (in the absence of resuscitative equipment or in unmonitored settings) and in patients with acute bronchial asthma or hypercarbia. Contraindicated in any patient who has or is suspected of having a paralytic ileus.	Contraindicated in patients who are hypersensitive to buprenorphine or naloxone.

Prescribing Considerations	Extended-Release Injectable Naltrexone	Methadone	Buprenorphine
Warnings	Use with caution in patients with active liver disease, moderate to severe renal impairment, and women of childbearing age. Discontinue in the event of symptoms or signs of acute hepatitis. As with any IM injection, extended-release injectable naltrexone should be used with caution in patients with thrombocytopenia or any coagulation disorder (e.g., hemophilia, severe hepatic failure); such patients should be closely monitored for 24 hours after naltrexone is administered. Patients may become sensitive to lower doses of opioids after treatment with extended-release injectable naltrexone. This could result in potentially life-threatening opioid intoxication and overdose if previously tolerated larger doses are administered. Clinicians should warn patients that overdose may result from trying to overcome the opioid blockade effects of naltrexone.	Methadone should be used with caution in elderly and debilitated patients; patients with head injury or increased intracranial pressure; patients who are known to be sensitive to central nervous system depressants, such as those with cardiovascular, pulmonary, renal, or hepatic disease; and patients with comorbid conditions or concomitant medications that may predispose to dysrhythmia or reduced ventilatory drive. Methadone should be administered with caution to patients already at risk for development of prolonged QT interval or serious arrhythmia. The label includes a warning about somnolence that may preclude driving or operating equipment.	Caution is required in prescribing buprenorphine to patients with polysubstance use and those who have severe hepatic impairment, compromised respiratory function, or head injury. Significant respiratory depression and death have occurred in association with buprenorphine, particularly administered intravenously or in combination with benzodiazepines or other central nervous system depressants (including alcohol). Buprenorphine may precipitate withdrawal if initiated before patient is in opioid withdrawal, particularly in patients being transferred from methadone. The label includes a warning about somnolence that may preclude driving or operating equipment.
Use in Pregnant and Postpartum Women	***Pregnancy:*** FDA pregnancy category C‡ ***Nursing:*** Transfer of naltrexone and 6ß-naltrexol into human milk has been reported with oral naltrexone. Because animal studies have shown that naltrexone has a potential for tumorigenicity and other serious adverse reactions in nursing infants, an individualized treatment decision should be made whether a nursing mother will need to discontinue breast feeding or discontinue naltrexone.	***Pregnancy:*** FDA pregnancy category C‡ Methadone has been used during pregnancy to promote healthy pregnancy outcomes for more than 40 years. Neonatal abstinence syndrome may occur in newborn infants of mothers who received medication-assisted treatment with methadone during pregnancy. No lasting harm to the fetus has been recognized as a result of this therapy but individualized treatment decisions balancing the risk and benefits of therapy should be made with each pregnant patient. ***Nursing:*** Mothers maintained on methadone can breastfeed if they are not HIV positive, are not abusing substances, and do not have a disease or infection in which breastfeeding is otherwise contraindicated.	***Pregnancy:*** FDA pregnancy category C‡ Neonatal abstinence syndrome may occur in newborn infants of mothers who received medication-assisted treatment with buprenorphine during pregnancy. No lasting harm to the fetus has been recognized as a result of this therapy but individualized treatment decisions balancing the risk and benefits of therapy should be made with each pregnant patient. ***Nursing:*** Buprenorphine and its metabolite norbuprenorphine are present in low levels in human milk and infant urine. Available data are limited but have not shown adverse reactions in breastfed infants.
Potential for Abuse and Diversion	No	Yes	Yes

SOURCES:[1,26–44]

‡ Animal studies have shown an adverse effect on the fetus and there are no adequate, well-controlled studies in humans, but potential benefits may warrant use of the drug in some pregnant women despite potential risks.

Extended-Release Injectable Naltrexone

The extended-release injectable formulation of naltrexone (Vivitrol®) was approved by the FDA in 2010 for the prevention of relapse to opioid dependence following opioid detoxification.[1] It is supplied as a 380 mg IM injection to be administered in the gluteal muscle every 28 to 30 days, alternating buttocks for each subsequent injection.

Packaging. The drug is packaged in a kit containing a vial of naltrexone microspheres as a dry powder, which must be suspended in a liquid diluent immediately before use. Kits must be refrigerated during storage but should be brought to room temperature approximately 45 minutes before an injection is given. The microspheres suspended in solution must be mixed vigorously to prevent clumping, which can clog the needle during injection.[27]

Each kit also contains a syringe and five needles—one for mixing the microspheres with the diluent and four needles (two 1.5-inch needles and two 2-inch needles) for injecting the suspension into the upper outer quadrant of the gluteal muscle.[27]

Formulation. Extended-release injectable naltrexone was developed by embedding the drug molecule in microspheres composed of a biodegradable copolymer, resulting in release of the active ingredient over a predetermined period. Upon injection, the microspheres begin to absorb water almost immediately, leading to a swelling of the microspheres. This process begins an initial release of the drug.

As water absorption continues, the polymer begins to undergo hydrolysis. Later, physical erosion of the polymer occurs. The drug diffuses into the surrounding media as the polymer continues to undergo hydrolysis and erosion, resulting in a sustained release of the drug from the microspheres. The polymer matrix eventually breaks down into lactic acid and glycolic acid, which are completely metabolized by the body and eliminated as carbon dioxide and water.

Pharmacodynamics and Pharmacokinetics. Naltrexone is a competitive antagonist at the opioid receptors in the brain. It is metabolized in the liver to the opioid antagonist 6-ß-naltrexol. The absorption of extended-release naltrexone is mediated by its gradual and prolonged release for 2 to 4 weeks after injection through hydrolysis of the copolymer microspheres.[27,45] Two peak blood levels occur after injection of the extended-release formulation: a transient initial peak occurs approximately 2 hours later and a second peak occurs about 2 to 3 days later. About 14 days after injection, the blood level slowly begins to decline in a linear fashion.

Efficacy. The phase 3 clinical trials of extended-release injectable naltrexone showed a consistent pattern of clinical efficacy for maintaining abstinence, achieving medication adherence, maintaining retention, protecting against reestablishment of opioid physical dependence, and may reduce craving for opioids for some individuals, while showing good safety and tolerability.[27,29]

Indications, Contraindications, and Cautions. The FDA-approved indication for extended-release injectable naltrexone is the prevention of relapse to an opioid use disorder following opioid detoxification.[27] Other information on indications, contraindications, and cautions appears in Table 1. It is advisable to download a copy of the full prescribing information from the FDA (available at http://www.fda.gov/safety/medwatch/safetyinformation/ucm208449.htm).

Safety. Based on its use in the treatment of alcohol dependence (an indication approved by the FDA in 2006), extended-release injectable naltrexone appears to be reasonably well tolerated. Its side effect profile is similar to that of oral naltrexone, with the addition of possible injection site reactions (ISRs).[1,46]

Side effects reported in clinical trials include nasopharyngitis, influenza, upper respiratory tract infection, sinusitis, insomnia, headache, dizziness, upper abdomen pain, diarrhea, fatigue, and back pain.[46–50] Muscle cramps, dizziness, sedation, decreased appetite, and an allergic form of pneumonia also have occurred in patients treated with extended-release injectable naltrexone, as have common cold symptoms, and toothaches.[1,27,28]

More serious adverse reactions, with advice on their management, include the following:

- *ISRs:* Extended-release injectable naltrexone injections may cause pain or tenderness at the injection site, which usually resolves in 2 to 5 days. However, more serious reactions such as swelling, erythema, bruising, and pruritus may occur, generally as the result of an inadvertent subcutaneous injection. Providers should be trained in proper techniques for IM injections to prevent problems.[45] The FDA issued an alert on this subject following phase 3 clinical trials because of reports of severe ISRs requiring surgical intervention.[46]
- *Vulnerability to opioid overdose:* Following a person's treatment with extended-release injectable naltrexone, his or her opioid tolerance is reduced from pretreatment baseline, and patients are vulnerable to potentially fatal overdose at the end of a dosing interval, after missing a dose, or after discontinuing treatment. Attempts to overcome the blockade may also lead to fatal overdose.
- *Hypersensitivity reactions, including anaphylaxis:* Trial results included reactions such as urticaria and angioedema. Patients should be warned of these risks and advised to seek immediate medical attention should any symptoms of hypersensitivity reactions arise.[27]
- *Hepatotoxicity:* Cases of hepatitis and clinically significant liver dysfunction were observed in association with extended-release injectable naltrexone treatment. Patients should be warned of the risk of such injury.[27,45]
- *Depression and suicidality:* Depression-related adverse events and events of a suicidal nature were observed in clinical trials of extended-release injectable naltrexone. Patients should be monitored for development of depression, suicidal thinking, or mood or anxiety disorders and treated appropriately, and families and caregivers should be alerted to the need to monitor patients for the emergence of depression or suicidality.[27,45]
- *Precipitated opioid withdrawal:* When withdrawal is precipitated abruptly by the administration of an opioid antagonist to a patient dependent on opioids, the resulting withdrawal syndrome can be severe enough to require hospitalization. An opioid-free interval is recommended for patients previously dependent on opioids. This interval should be guided by the type of opioid that the patient had been taking previously—that is, short- or long-acting opioids. Health care providers should always be prepared to manage withdrawal symptomatically. Patients should receive supportive treatments (i.e., hydration and antispasmodic and antidiarrheal medications) until opioid withdrawal symptoms resolve. Benzodiazepines or ∂2-agonists such as clonidine should mitigate some withdrawal symptoms (watch for side effects of clonidine, including dizziness, hypotension, fatigue, and headache).

Drug Interactions. Patients taking naltrexone may not experience pain relief from opioid-containing medications because naltrexone antagonizes the opioid effects.[27]

Clinical Recommendations. Although no definitive research supports which patients benefit most from extended-release injectable naltrexone, patients in the following categories may be good candidates for such treatment.[1]

- *Patients who have not had treatment success with methadone or buprenorphine:* Depending on the reasons for treatment failure, individuals with an opioid use disorder who have not been successfully treated with methadone or buprenorphine may benefit from medically supervised withdrawal followed by a trial of extended-release injectable naltrexone.[51]
- *Patients who have a high degree of motivation for abstinence:* Individuals who are highly motivated to achieve and maintain abstinence from opioids may be good candidates for treatment with extended-release injectable naltrexone.[50] This category includes people who are required to demonstrate abstinence on urine drug screens, such as individuals in programs for impaired health care professionals, parolees, probationers, and airline pilots.[52]
- *Patients who have been successful on opioid agonists who wish to discontinue agonist therapy or patients who are not interested in*

agonist therapy to treat their opioid use disorder: Some patients may be successful on agonist treatment and want continued pharmacologic help to prevent relapse but prefer another type of treatment.[51] Other patients may not be interested in agonist therapy.[1] The latter group typically includes individuals who (1) feel they are discriminated against (or are embarrassed or ashamed) because they are on agonist therapy[53] or (2) would like to reduce the time devoted to daily or multiple OTP visits per week, as is frequently required for methadone treatment.[1]

Patients may be suitable candidates for treatment with extended-release injectable naltrexone even if past episodes of medication-assisted treatment were not successful.[54] However, experts agree that the following patients are unlikely to do well on extended-release injectable naltrexone:[1]

- Patients who do not tolerate extended opioid-free periods. For example, a patient who is not tolerating withdrawal is better managed with a partial agonist (buprenorphine) or an agonist (methadone) than with an antagonist medication.
- Patients who are unable to complete withdrawal.
- Patients who experience protracted abstinence symptoms following withdrawal.
- Patients whose psychiatric symptoms worsen during withdrawal.
- Patients whose chronic pain requires treatment with opioid analgesics. Treatment with extended-release naltrexone is not a viable option if pain requires chronic opioid therapy.
- Patients who have advanced liver disease, impending liver failure, or acute hepatitis. Use of extended-release injectable naltrexone probably is safe in patients with chronic hepatitis B or C provided that the patient is not at the end stage and starting to go into liver failure. Patients with routine elevated liver enzymes usually tolerate naltrexone

Integrating Pharmacologic and Nonpharmacologic Therapies

Some patients respond to psychosocial interventions or medication therapy alone, but most patients need both. The different approaches (medication-assisted treatment, professional counseling, and mutual-help groups) are complementary. They support the same goals while addressing different aspects of opioid use disorder: neurobiological, psychological, and social.

Offering the full range of effective treatments maximizes patient choice and outcomes, because no single approach is universally successful. Many studies show that the combination of pharmacologic and nonpharmacologic interventions may be more effective than either approach used alone.[55]

Sources of information on psychosocial therapies suitable for patients being treated in medical office settings are shown in Appendix B.

Encouraging Participation in Mutual-Help Programs. The support of a mutual-help group can be critical to long-term recovery. The oldest, best-known, and most accessible mutual-help program for people with an opioid use disorder is offered by NA. Patients may resist attending NA meetings and may fear that disclosure of medication use will make them unwelcome.[26] Although some NA members may have negative attitudes toward medication, the organization itself supports appropriate medication use. Providers should encourage patients to try meetings of different groups until they find one that is a good fit. Lists of local meetings to give to patients can be obtained from the Narcotics Anonymous World Services Web site (http://www.na.org).

Other mutual-help groups, although not as universally available as NA, have a strong presence in many communities. Contact information for several groups that may be helpful to patients and their families is provided in Appendix B.

The support of a mutual-help group can be critical. The oldest, best known, and most accessible mutual-help program for people with an opioid use disorder is offered by Narcotics Anonymous.

Special Considerations in Treatment Planning

Some patients present with specific conditions or at life stages that require special consideration in formulating a treatment plan.

Patients With Psychiatric Comorbidities. Studies of treatment populations have shown that co-occurring psychiatric disorders are present in 20 percent to 60 percent of people entering treatment, depending on the treatment group of the study and its methodology.[56] Even higher rates have been reported among older adults, people with low socioeconomic status, and those who reside in urban areas,[57,58] as well as those who are homeless[59] or incarcerated.[60]

When psychiatric and substance use disorders co-occur, the two disorders typically become intertwined, thus complicating the treatment plan and process. Therefore, whenever a patient enters treatment for either a substance use disorder or a psychiatric disorder, he or she should be assessed for the co-occurrence of the other.[24] To establish how a patient's substance use and a psychiatric disorder are linked, the order of onset of their psychiatric disorder and substance use, family history, and effect of previous treatments of the co-occurring psychiatric disorder should be determined.[54]

Patients With Co-Occurring Medical Disorders. Individuals with substance use disorders almost always are at higher risk for disease and other medical disorders than are those without addiction disorders. Furthermore, people with substance use disorders typically miss opportunities to receive preventive health care.[22,61]

Like individuals with other chronic medical conditions, those who misuse opioids exist on a continuum ranging from less to more medically complicated.[52,62,63] Moreover, the management of unrelated medical illnesses is complicated by addiction, its effect on adherence to the treatment regimen, and the direct consequences of the misused substances. This complication warrants a targeted approach to the conditions for which a patient is at risk.[22]

Hepatic disorders: Hepatic monitoring is important because HCV seroprevalence is high among people with opioid use disorder. The U.S. Departments of Veterans Affairs and Defense guidelines for the use of naltrexone recommend measuring baseline transaminase levels, followed by periodic monitoring at 6- or 12-month intervals.[64]

HIV/AIDS: Methadone interacts with several antiretroviral treatments for HIV, buprenorphine causes fewer concerns, and extended-release injectable naltrexone causes almost none.[65] However, treatment is worth considering because of the prevalence of HIV infection among people who inject drugs.

Pain: Because of their opioid agonist activity, methadone and buprenorphine offer advantages in treating patients who have chronic pain. Naltrexone is not a good choice for people whose pain needs to be treated with opioid analgesics, but it can be used in patients whose pain is treated with non-opioid analgesics.

Obesity: In obese patients, a longer needle is needed to reach the muscle with injections. The risk of rare aseptic abscesses and other severe ISRs may increase when the injection goes subcutaneously into fatty tissue instead of the muscle.

Renal disorders: Renal problems do not require dose adjustments with naltrexone or buprenorphine.

Hospitalization: If a patient who is taking extended-release injectable naltrexone is hospitalized for medical reasons, special attention must be directed to the provision of adequate pain control.[22]

Alcohol dependence: Extended-release injectable naltrexone has dual activity for the prevention of relapse to both high-risk drinking and opioid use.

Marijuana use: Patients who use marijuana or other substances containing tetrahydrocannabinol may need other types of pharmacotherapy until research studies clearly show whether extended-release injectable naltrexone increases the cardiovascular risks of cannabinoids.[66]

Adolescents. The lack of treatment resources geared specifically to young people, coupled with the epidemic of prescription opioid and heroin abuse in this population, has left many young people with few effective treatment options.[67]

Ample evidence demonstrates the failure of detoxification-only treatments and the high rates of dropout from psychosocial-only treatments on the part of adolescents and young adults. Yet, despite an increasing body of evidence that medications such as buprenorphine, methadone, and naltrexone are effective and easily combined with psychosocial treatments, only buprenorphine is approved by the FDA for the treatment of patients younger than 18, and the safety and effectiveness of buprenorphine hydrochloride sublingual tablets in patients younger than 16 have not been established. Therefore, the best course of action is to refer young patients to an addiction specialist or program with experience in treating adolescents.[5]

Pregnant and Postpartum Women. Opioid use disorder is associated with increased maternal and neonatal complications.[54] Currently, no medications have been approved by the FDA for treatment of opioid use disorder during pregnancy. Treatment with methadone or buprenorphine has been used, but the risks are not known.[68–70] Although there is some interest in the potential for extended-release injectable naltrexone in this population, no research to evaluate its safety or efficacy has been conducted to date.[71]

FDA-approved prescribing information for extended-release injectable naltrexone states that "there are no adequate and well-controlled studies of either naltrexone or extended-release injectable naltrexone (Vivitrol®) in pregnant women. This product should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."[27] Accordingly, patients dependent on opioids who are pregnant or nursing should be referred to an addiction specialist or program with experience in treating this population.

Older Adults. Members of the baby boom generation had more experience with nonmedical drug use than members of prior generations, and this continues to be true as members of this population reach retirement age and experience consequences of aging such as chronic pain. Furthermore, substance use disorders in older adults often are misdiagnosed, as are the consequences of such disorders.[54] For example, dementia, malnutrition, self-neglect, functional decline, sleep problems, and anxiety or depression all may be attributed to "normal" aging when the true cause is substance misuse or a substance use disorder.[22]

Studies show that older adults can and do benefit from treatment and in some cases have better outcomes than do younger adults.[72] However, there are few studies of extended-release injectable naltrexone in this population.

In the absence of a specific evidence base for naltrexone in older adults, pharmacologic treatments should follow the evidence base for the general adult population. Health care providers may need to consider using oral naltrexone if the fixed dose extended-release injectable naltrexone is not appropriate in elderly patients with age-related pharmacokinetic and pharmacodynamic changes, as well as any mental or physical comorbidities.[54]

Studies show that older adults can and do benefit from treatment and, in some cases, have better outcomes than do younger adults.

Other Populations. Certain highly motivated licensed individuals, such as health care professionals, attorneys, and pilots, may be ideal candidates to accept and persist with treatment with extended-release injectable naltrexone.[52,73] Many professional groups have specialized programs that promote treatment, monitor recovery, and provide advocacy to maintain licensure. It has been suggested that professional advocacy might be the "voucher" or "contingency" that makes compliance with extended-release injectable naltrexone worthwhile for licensed professionals with opioid use disorder.[74] For example, some clinical evidence suggests that this may be the case with anesthesiologists.[75]

In contrast, some individuals who are relatively less motivated or at an early stage in the addiction process may need specific counseling approaches to addressing their motivational issues before treatment with extended-release injectable naltrexone is initiated.[76]

INITIATING MEDICATION–ASSISTED TREATMENT

Educating the Patient and Obtaining Informed Consent

The clinician should discuss with the patient the risks and benefits of medication-assisted treatment as compared with the risks associated with no treatment or treatment without medication.[4,77–80] In addition, certain topics should be reviewed with every patient who is a candidate for medication-assisted treatment.[81] Face-to-face conversations, supplemented by written fact sheets, are helpful in answering the following questions:

- Which medication is to be used? How is it administered? How does it work? What are its advantages and disadvantages?
- What is the duration of treatment, its cost, and associated routines?
- What are the known side effects?
- What are the contraindications?
- What are the issues related to pregnancy, lactation, and contraception?
- What are the dangers of concurrent use of nonprescribed drugs?
- What are the potential interactions between extended-release injectable naltrexone and other therapeutic medications?
- What is the potential impact of treatment with extended-release injectable naltrexone on driving, other activities of daily living, and employment?

Because methadone normalizes endocrine functions, it is not unusual for women in the early phases of medication-assisted treatment to become pregnant unintentionally, especially if they do not receive counseling for this possibility.[82]

Patients should be educated about the effects of using opioids and other drugs while taking the prescribed medication and the potential for overdose if opioid use is resumed after tolerance is lost.[83,84] Some health care providers supply a laminated card that identifies the individual as a patient of their practice. This is helpful to other health care providers who may see the patient in an emergency department.[24]

Informed Consent. The patient's informed consent to treatment should be documented in a written form that is discussed with and signed by the patient. Such a form can be helpful in reinforcing the information provided and establishing a set of ground rules. Typical provisions of an informed consent document include:[17]

- The medication and other therapies to be employed, with a rationale for their use
- Schedules for follow-up office visits and laboratory testing to monitor the patient's progress and health status
- Goals for attendance at meetings of mutual-help groups
- Involvement of family or significant others in treatment
- Symptoms that should be reported to the prescribing physician
- A plan for treating any co-occurring medical or psychiatric conditions, as well as other substance use disorders, including smoking
- Criteria for discontinuing the use of medication or other therapies and referral to specialty addiction treatment, if indicated

The patient should be advised to carry a medical alert card identifying the use of extended-release naltrexone, describing any potential adverse effects, and providing contact information for the treating clinician or institution in an emergency.[17]

> *The patient should be advised to carry a medical alert card identifying the use of extended-release naltrexone, describing any potential adverse effects, and providing contact information in an emergency.*

The fact that a patient has received and understands this information should be documented in a written informed consent agreement, which should be signed before treatment is initiated and filed in the patient's medical record.[17]

Withdrawing the Patient From Opioids

Naltrexone displaces heroin or prescribed opioids from receptors to which they have bound, so it can precipitate significant withdrawal symptoms. Therefore, it is important that detoxification from

opioids be completed at least 7 to 10 days before extended-release injectable naltrexone is initiated or resumed. A urine drug screen to confirm abstinence should be conducted before naltrexone is started.[27] Patients who are transitioning from buprenorphine or methadone to naltrexone may be vulnerable to precipitation of withdrawal symptoms for as long as 2 weeks. Clinicians should be prepared to manage withdrawal symptomatically with non-opioid medications.[27]

The withdrawal syndrome that occurs spontaneously is marked by a predictable constellation of signs and symptoms that follow a rapid decrease in, or abrupt discontinuation of, intake of an opioid that has been used consistently for a period of time.

The withdrawal syndrome that occurs spontaneously is marked by a predictable constellation of signs and symptoms that follow a rapid decrease in, or abrupt discontinuation of, intake of an opioid that has been used consistently for a period of time.[85]

Some patients experience prolonged withdrawal signs or symptoms, known as *protracted abstinence syndrome*. Symptoms of the syndrome include sleep disturbances, anxiety, irritability, and mood instability.[1] Suggested nonpharmacologic approaches include educating patients about expected symptoms, offering support and understanding, monitoring the patient for sleep disturbances or co-occurring disorders, encouraging physical and mental activities, and promoting the use of mutual-help groups. For some patients with protracted withdrawal, additional psychosocial interventions (such as cognitive behavioral therapy) or pharmacotherapy may be necessary to avoid relapse.[86]

Precipitated withdrawal is much more severe than spontaneous withdrawal, and patients undergoing precipitated withdrawal can become very ill. Patients must understand that withdrawal precipitated by administration of an opioid antagonist may be severe enough to require hospitalization if they have not been opioid free for an adequate period and is different from the experience of spontaneous withdrawal that occurs with discontinuation of opioid in an individual with an opioid use disorder.

Bell and colleagues[87] suggested that following one of the following two approaches to induction into naltrexone treatment can help avoid precipitated withdrawal:

1. The conventional approach is to undertake detoxification and, when patients have been free of opioids for 7 to10 days or free of methadone for 10 days, begin treatment with naltrexone. Patient histories can be unreliable, so it is advisable to perform a naloxone challenge test before giving the first dose of naltrexone to avoid inadvertently precipitating a significant or prolonged withdrawal reaction. Patients may experience precipitated withdrawal despite tolerating a naloxone challenge test.
2. Antagonist-accelerated induction (rapid detoxification[*88]) involves administration of naltrexone or naloxone, while providing symptomatic relief to make the ensuing precipitated withdrawal tolerable. See footnote for cautions on this procedure issued by the Centers for Disease Control and Prevention (CDC)[88]

Health care providers should always be prepared to manage precipitated withdrawal, even if the steps identified above are taken.

Reported cases of precipitated withdrawal have frequently involved patients transitioning from buprenorphine.

Successful management of withdrawal can facilitate entry into addiction treatment by reducing uncomfortable withdrawal symptoms that negatively reinforce drug taking. This is best managed by a specialized practitioner or treatment program.[5]

Many individuals undergo withdrawal more than once, and some do so many times. When people who were recently dependent return for repeat detoxification they do so generally with a more

[*] Anesthesia-assisted rapid opioid detoxification (AAROD) for the purpose of induction onto naltrexone carries additional risks, including death. The CDC advises against the use of AAROD because of these risks and the fact that less risky yet effective protocols are available for detoxification and maintenance pharmacotherapy.[88]

realistic expectation of what is needed to remain free from alcohol and drugs.[89]

People in the early stages of treatment often relapse to substance use and get caught up in a revolving door of repeated detoxification. Therefore, it is important to educate patients that short-term treatment of withdrawal does not eliminate the need for long-term treatment of addiction.[5,77,90]

Induction Onto Extended-Release Injectable Naltrexone Treatment

The clinician should consider how best to induct a patient into treatment with extended-release injectable naltrexone. Product labeling and standard practice call for 7 to 10 days of abstinence from short-acting opioids before starting naltrexone.[91] A urine drug screen should be conducted to verify abstinence before beginning induction.[51]

Dosing and Administration. For patients who are appropriate candidates, the recommended dose of extended-release injectable naltrexone is 380 mg, delivered intramuscularly approximately every 30 days, alternating buttocks for each subsequent injection. The following cautions should be observed:[1,83,92]

- Injectable naltrexone should be administered only by a medical professional (a physician, nurse, or physician assistant) who knows how to administer IM gluteal injections.
- Injectable naltrexone is packaged in a kit containing a vial of naltrexone microspheres as a dry powder that must be suspended in a liquid diluent immediately before use. Kits must be refrigerated during storage but should be brought to room temperature approximately 45 minutes before an injection is given. The powder and diluent must be mixed vigorously to prevent clumping, which can clog the needle during injection.
- A syringe and five needles are provided—one for mixing the microspheres with the diluent and four (two 1.5-inch needles and two 2-inch needles) for injecting the suspension into the upper outer quadrant of the gluteal muscle. Body habitus should be assessed before each injection for each patient to ensure that needle length is adequate for IM administration. Injectable naltrexone must be administered only with one of the administration needles supplied in the carton. A spare administration needle of each size is provided in case of clogging.
- Proper IM injection technique is essential. Serious ISRs, some requiring extensive surgical debridement, have been observed with extended-release injectable naltrexone. It has been reported that likelihood of these severe reactions may increase if the product is inadvertently administered subcutaneously rather than intramuscularly.
- The medication should be administered every 4 weeks. If a dose is delayed or missed, the next injection should be administered as soon as possible. However, it is not recommended that medication be readministered at less than 4-week intervals.
- It is not recommended that the medication be administered at a dose higher than 380 mg.

Following IM injection, the plasma concentration time profile is characterized by a transient initial peak at about 2 hours after injection, followed by a second peak approximately 2 to 3 days later. At approximately 14 days after administration, concentrations begin to slowly decline, with measurable levels detectable for more than 30 days after administration. However, the therapeutic benefit of a single dose has not been established for periods longer than 4 weeks.[27]

Supportive Care Following Induction. Careful follow-up is a critical element in optimizing the benefits of naltrexone treatment. The practitioner performing induction onto naltrexone treatment should schedule two office visits in the first week of induction to assess the patient. Weekly clinical reviews should be conducted in the first month of treatment. Other elements of supportive care include the following:[87]

- Medical monitoring such as a regular review by the prescribing physician, with monitoring of compliance, review of drug use, and sometimes urine drug screens to confirm self-report
- Counseling in regularly scheduled sessions with a professional counselor
- Mutual-help groups and family involvement

Transfer to Extended-Release Injectable Naltrexone. If a patient is being transferred to extended-release injectable naltrexone from methadone or buprenorphine, the taper should be completed 7 to 10 days before naltrexone induction begins.[27]

Special Considerations in Pain Management. Extended-release naltrexone blocks the effects of opioid analgesics. For acute pain (e.g., that associated with dental work, surgery, traumatic injury), regional analgesia, conscious sedation, use of non-opioid analgesics, or general anesthesia may be needed for pain management.[24,83]

If regional anesthesia is not used, then a larger amount of opioid analgesic may be needed to override the opioid blockade, but this should be done in a hospital setting because it may result in respiratory depression that is deeper and more prolonged than usual. For this reason, a rapid-acting opioid analgesic that minimizes the duration of respiratory depression is preferred. The amount administered should be titrated to the needs of the patient. In such cases, the patient should be monitored closely by trained medical personnel.[5,24]

Careful follow-up is a critical element in optimizing the benefits of naltrexone treatment. The practitioner performing induction onto naltrexone treatment should schedule two office visits in the first week of induction to assess the patient. Weekly clinical reviews should be conducted in the first month of treatment.

MONITORING PATIENT PROGRESS AND ADJUSTING THE TREATMENT PLAN

As with patients with other chronic relapsing disorders, patients diagnosed with opioid use disorder require long-term monitoring and support, as well as periodic adjustment of the treatment regimen.

Monitoring Patient Progress

Use of medication-assisted treatment requires careful monitoring throughout treatment, with special attention to problems that may arise at the time of induction.

Monitoring patient progress is an ongoing process that assesses the patient on four dimensions:[5] (1) adherence to the treatment plan, (2) ability to maintain abstinence, (3) levels of craving, and (4) overall health status and social functioning. Toxicology screening is an important part of monitoring patient compliance and progress. At each visit, the health care provider should:

- Assess the patient for continued use of any illicit or nonprescribed drug
- Assess the patient's adherence to the treatment regimen
- Assess changes in the patient's social functioning and relationships
- Review whether the patient is involved in counseling
- Monitor for side effects of the extended-release injectable naltrexone and other prescription medications

With this information, the clinician can decide whether to continue pharmacotherapy, modify the treatment plan as indicated, and address any co-occurring medical, psychiatric, and substance use issues.

Sources of Information. Patient self-reports can be useful indicators of treatment progress. In eliciting such information, it is important to avoid conveying a judgmental attitude toward the patient's behavior. The clinician should ask about the quantity and frequency of alcohol and drug use, especially during stressful periods (e.g., holidays, celebrations, major life changes). The patient also should be asked about current craving and how he or she felt over the preceding week (by assigning a rating between 1 and 10, with 1 indicating no craving and 10 the most

intense craving the patient has ever experienced). In addition, the patient may be asked whether any episodes have caused particular problems. Identifying patterns of craving over time allows both the clinician and the patient to see that the patient's patterns of craving may fluctuate throughout the day and over longer periods, indicating the need to continue, adjust, supplement, or discontinue use of a particular medication.

Other sources and types of information that are useful in patient monitoring include the following:[5,17]

- Laboratory tests, such as the ALT, AST, GGT, CDT, and random urine drug screens, including ethyl glucoronide, to detect recent alcohol use
- The patient's history of keeping (or not keeping) appointments for office visits, following-up on referrals, or attending mutual-help groups
- Data from the state PDMP (if available) on the patient's use of prescribed opioids or other prescribed medications
- Information about other nonprescribed drugs being used
- Reports from family members (obtained with a signed release from the patient)
- Periodic status reports from consultants on the patient's use of psychosocial therapies or other supports

Opioid use disorder is a chronic illness that, despite treatment, may wax and wane in intensity over time.

Documenting Patient Progress. In the event of a legal, regulatory, or civil (malpractice-related) challenge, detailed medical records documenting what was done and why are the foundations of the practitioner's defense. Every clinician needs to be aware of and understand the federal requirements for recordkeeping, as well as the laws and regulatory requirements of the state in which he or she practices.[17] State laws and medical board rules may differ substantially from federal requirements and from one state to another. The board of medical licensure or board of pharmacy in each state can provide information about relevant requirements. At a minimum, patient records should contain the following information:[93,94]

- *Patient history and physical examination:* The patient's record must include a history of all controlled drugs used to treat the patient, a history of illicit substances used, and patient allergies. Past treatment attempts also should be documented. Medical records obtained from clinicians who have treated the patient in the past should be included. (Caution should be exercised in accepting records supplied by patients, because these occasionally are fraudulent.) The medical record also should include information about the patient's personal and family history of alcohol, tobacco, and other substance use as well as a personal history of major depression or other psychiatric disorder.
- *Treatment plan:* The treatment plan and goals should be documented in the record so that there is evidence of clear-cut, individualized objectives to guide the choice of therapy. Patient improvements after a brief trial should be documented in the record, as should all regimens that were tried but failed.
- *Consultants' reports:* Whenever the best clinical course is not clear or the patient's response is not as expected, consultation with an appropriate specialist should be obtained. Generally, the results of the consultation should be discussed with the consultant and a written consultation report should be added to the patient's medical record.
- *Prescription orders:* The patient record must include all prescription orders, whether written or telephoned. Written instructions for the use of all medications should be given to the patient and documented in the record. The prescription order should list medication name, formulation, route of administration, and amount.
- *Informed consent:* A written informed consent or treatment agreement signed by both patient and practitioner can be helpful in establishing a set of ground rules and appropriate expectations.
- *Monitoring visits:* Medication monitoring visits are billable and can be performed by a nurse. They should be carefully documented in the medical record, in the same manner as a visit with the physician.

- *Treatment progress/outcomes:* The patient's record should clearly reflect the decision-making process that led to a medical, psychiatric, or behavioral outcome.

> *A patient's goals may change over time, requiring the clinician to adapt to new objectives.*

Good records demonstrate that a service was provided to the patient, and that the service was medically necessary. Even if the outcome is less than optimal, thorough records protect the clinician as well as the patient.[94]

Adjusting the Treatment Plan

Opioid use disorder is a chronic illness that, despite treatment, may wax and wane in intensity over time.[5] If a patient begins to experience problems with adherence, the clinician should revisit the treatment plan to determine whether different strategies or treatment modalities (pharmacologic and nonpharmacologic) might be useful. For example, switching the patient from oral naltrexone to extended-release injectable naltrexone may enhance compliance with medication use.

A patient's goals also may change over time, requiring the clinician to adapt to new objectives. Also, as with patients who receive treatment for other chronic diseases, patients receiving treatment for an opioid use disorder may relapse.

Responding to Changes in Treatment Progress. Individuals receiving medication-assisted treatment often demonstrate dramatic improvement in addiction-related behaviors and psychosocial functioning. Such positive changes should be acknowledged and reinforced by the prescribing physician whenever possible.[10,95]

However, lack of adherence to pharmacologic regimens occurs in a substantial proportion of patients, with some studies reporting that as many as 7 out of 10 patients fail to follow the treatment plan.[5] If a patient experiences problems with adherence, the clinician should revisit the treatment plan to determine whether different strategies or treatment modalities (pharmacologic or nonpharmacologic) might be useful. Other strategies to improve adherence and reduce the risk of relapse during treatment include providing incentives to take the monthly injections (i.e., contingency management); involving significant others in monitoring the patient to ensure adherence to the medication plan, in a manner consistent with patient privacy requirements; offering relapse prevention counseling; and using motivational interviewing techniques.[44,47,96]

Behaviors that violate the treatment agreement or that indicate limited progress in treatment may not constitute grounds for automatic termination of medication-assisted treatment. Such behaviors should trigger a reassessment of the patient's needs and goals and a corresponding revision of the treatment plan. Aberrant or dysfunctional behaviors may indicate the need for more vigorous engagement in peer support, counseling, or psychotherapies or possibly referral to a more structured treatment setting.[55]

Alternative pharmacologic therapies such as methadone or buprenorphine maintenance therapy also should be considered for these patients.[27,84] Such changes should be documented in the patient's medical record.[10]

> *Relapse rarely is caused by a single factor and often is the result of an interaction of physiologic and environmental factors. It is best conceptualized as a dynamic process in which the patient's readiness to change interacts with other external and internal factors.*

Preventing and Responding to Relapse. As with patients who receive treatment for other chronic disorders, patients receiving treatment for an opioid use disorder may experience relapses. Relapse rarely is caused by a single factor and often is the result of an interaction of physiologic and environmental factors.[97] It is best conceptualized as a dynamic process in which the patient's readiness to change interacts with other external and internal factors.[98]

If relapse occurs, the clinician should consider several options:

- Examine social, medical, or behavioral factors that contribute to the patient's substance use
- Increase monitoring
- Change the medication

- Increase or change the intensity of psychosocial services
- Refer the patient for specialty care

Relapse risk is highest in the first 6 to 12 months after achieving abstinence and then diminishes gradually over the years. It may be necessary to escalate other treatment or to resume therapy with extended-release injectable naltrexone services if relapse appears imminent. Patients should be cautioned that they will be more sensitive to lower doses of opioids after treatment with extended-release injectable naltrexone is discontinued.[24]

Reinduction Onto Naltrexone Treatment. Many patients who have relapsed express a desire to resume naltrexone treatment. If a patient experiences multiple relapses, the clinician should consider whether to continue treatment with naltrexone or whether to offer a different treatment modality.

Patients may benefit from referral to a specialist for additional evaluation and treatment. For example, the treatment of addiction for a patient with a comorbid psychiatric disorder may be best managed through consultation with or referral to a specialist in psychiatry or addiction psychiatry.[99]

DECIDING WHETHER AND WHEN TO END MEDICATION-ASSISTED TREATMENT

Long-term treatment, which is common to many chronic medical conditions, should not be seen as a failure. In fact, it is a cost-effective way of prolonging life and improving the patient's quality of life by supporting the natural and ongoing process of change and recovery.[24] Nevertheless, the physician and patient may wish to weigh the potential benefits and risks of continuing medication-assisted treatment and discuss whether such therapy remains appropriate.

Factors to consider in determining a patient's suitability for long-term, medication-free status include the presence of stable housing and income, availability of adequate psychosocial supports, and the absence of legal problems. For patients who have not achieved these indices of stabilization, a period of maintenance to address these barriers usually is advised.[55]

Ideally, the patient and practitioner will reach a decision about whether and when medication-assisted treatment should be discontinued, usually for one of the following reasons:[24]

- The patient reports substantially diminished craving.
- The patient has maintained stable abstinence over a sustained period.
- The patient feels ready to discontinue the medication.
- The patient is engaged in ongoing recovery, including community supports (such as attendance at mutual-help group meetings).

Less than ideally, some patients simply stop taking their medication without consulting the prescriber. Alternatively, a patient may ask to discontinue medication use because of side effects or other reasons. Still other patients must discontinue medication use because of a significant negative laboratory finding or problem with their physical health status.[5,24]

The clinician should help the patient withdraw from the medication at an appropriate pace and encourage the patient to continue with psychosocial therapies and participation in mutual-help groups. In the case of extended-release injectable naltrexone, withdrawal is termination of the monthly injection. Patients who resist treatment should be reassessed for co-occurring disorders.

If the patient wishes to continue treatment, his or her engagement in counseling and other psychosocial services should be intensified.[100] However, if the patient does not want to continue treatment, the physician may consider referring him or her to an addiction specialist or treatment program.[17]

Relapse can be fatal. Patients who relapse to opioid use after being treated with extended-release injectable naltrexone or other medications

are at risk for accidental overdose and overdose-related death.[101] If a patient reverts to pretreatment opioid use, as the blockade wanes, he or she may experience overdose and life-threatening consequences, including respiratory arrest and circulatory collapse.[27] Therefore, it is recommended that clinicians and patients jointly develop a relapse prevention plan.[84] SAMHSA's Opioid Overdose Toolkit[102] includes strategies for developing such a plan that includes ways to address emergency reversal of actual or suspected opioid overdose (see Appendix B for more information).

Relapse to drug use often is preceded by emotional and cognitive relapse. Negative mood states may be warning signs of impending relapse, as are behaviors such as isolating or overcommitting oneself or failing to maintain healthful sleeping and eating habits. People in recovery may need to plan how to respond to disappointments and celebrations without relapsing to drug use.

Cognitive patterns that may predict relapse include thinking that others are having more fun, glamorizing past drug use, and seeing opportunities to relapse without getting caught when others are otherwise occupied or away. The relapse prevention plan should include strategies for managing these thoughts when they arise, such as contacting a supportive person, imposing a specific waiting period before acting, distracting oneself with physical or enjoyable activities, making a list of the pros and cons of drug use, and deciding not to use drugs "just for today."

Although relapse may be seen as a normal part of a chronic medical disorder, relapse to using opioids after a period of abstinence is strongly associated with overdose. Patients should understand that medication treatment can be resumed if they find themselves unable to cope with negative moods or thoughts.

Every effort should be made to avoid secretiveness and shame about relapse. Providers may wish to consider providing newly medication-free patients with naloxone and supporting their family and friends in learning how to use it. This effort conveys the message that relapse may occur but that the patient has the opportunity to reenter treatment alive and well.

Voluntary Termination of Medication-Assisted Treatment

When the patient and physician agree to discontinue medication-assisted treatment, medically supervised withdrawal should be followed by long-term, drug-free treatment to minimize the risk of relapse.

Both the physician and the patient should accept that the patient may need or want to resume medication-assisted treatment, either with extended-release naltrexone or with another medication.[100] Patients also should be assured that relapse need not occur for them to be reinstated on medication-assisted treatment.[10]

If the best clinical course is not clear, consultation with a specialist may be helpful. The results of the consultation should be discussed with the patient and added to the patient's record.[25]

Referring a Patient for More Intensive Care

If office-based interventions are not effective for a given patient or if the clinician does not have the resources to offer needed care, the patient should be referred for more intensive or specialized services. Many specialty treatment programs provide services that address withdrawal and craving; management of long-term abstinence through pharmacotherapy; case monitoring; individual, group, and family/couples counseling and therapy; other psychosocial services such as vocational counseling; and referral to mutual-help groups.[5]

Specialized treatment programs anywhere in the United States can be identified through use of the Substance Abuse Behavioral Health Treatment Services Locator on the SAMHSA Web site at http://www.findtreatment.samhsa.gov.

A physician who is planning to treat a patient for opioid use disorder should become familiar with local treatment resources. Developing relationships with such specialized practitioners and programs facilitates the process of consultation and referral. In addition, understanding a program's treatment duration, modality, philosophy, and continuing-care options helps the physician identify appropriate placements for patients who no longer are

candidates for treatment in the general medical office.

A patient may become a candidate for referral to a more structured treatment environment (such as an OTP) for the following reasons:

- *Noncompliance with the treatment plan:* For example, a patient may continue to misuse opioids or fail to appear for scheduled monthly doses of extended-release injectable naltrexone. In such a situation, it may be advisable to transfer the patient to another medication or to refer him or her to a specialized practitioner or treatment setting for more intensive care.
- *Noncompliance with agreed-on activities:* A patient who refuses to participate in counseling or mutual-help groups may need more structure than can be provided in a general medical office and may be better served by an addiction specialist or in an OTP.
- *Threats or verbal abuse:* The patient who verbally abuses office staff, exhibits out-of-control behavior, or otherwise threatens the safety and well-being of office personnel or other patients is a special concern. Such a patient requires more structure than can be provided in a general medical office and should be referred to an addiction specialist or OTP.
- *Nonpayment for services:* If payment is owed for a backlog of bills and the patient has made no effort to arrange a payment plan or to access resources for payment, treatment termination may be necessary but should be done with care to ensure the patient does not leave without treatment options (i.e., patient abandonment).

Conditions that result in termination of treatment in a general medical office setting should be outlined in the treatment agreement or informed consent.[99]

Special Considerations

Situations that may require additional arrangements or a delay in referring or discharging a patient include the following:[99]

- If the patient is in an acute phase of treatment, termination must be delayed until the acute phase has passed. If the practitioner is the only source of treatment for the patient's opioid use disorder in a reasonable driving distance, the practitioner may need to continue care until other arrangements can be made.
- If the practitioner is the only source of a particular type of specialized medical care, he or she may need to continue care until the patient can be safely transferred to another practitioner who can provide such care.
- If the patient is a member of a prepaid health plan, the patient cannot be discharged until the practitioner has communicated with the third-party payer to ask that the patient be transferred to another practitioner.

It may become necessary to reinstate pharmacotherapy with extended-release injectable naltrexone or another medication or to provide other treatment services if relapse appears imminent or occurs.[25]

Documenting the Decision and Notifying the Patient

When terminating the physician–patient relationship (and no special considerations are present), the reasons for such termination should be formally documented in the patient record.

The patient also should be given a written notice that he or she must find another health care provider within a stipulated period. The notice should be mailed to the patient by certified mail, return receipt requested. Copies of the letter should be filed in the patient's medical record, along with the original certified mail receipt and the original certified mail return receipt (even if the patient refuses to sign for the certified letter).[10,25]

SUMMARY

Medication-assisted treatment has shown much promise in reducing nonmedical use of opioids and restoring patients to a healthier life. Considerable research evidence and consensus among experts support the use of pharmacologic treatments for an opioid use disorder in primary care settings. In fact, primary care physicians and members of their health care provider teams are ideally situated to employ these medications to help their patients—particularly those who have been unwilling or unable to access treatment in specialized settings—achieve and sustain a robust recovery from drug use and a safer, healthier life.

A number of FDA-approved medications have been shown to be important elements of such treatment. Although some patients do not benefit from medication-assisted treatment, most do. For each patient deemed an appropriate candidate for such treatment, multiple pharmacologic agents offer a variety of options so that treatment can be tailored to each patient's needs and circumstances.

Medication-assisted treatment has shown much promise in reducing nonmedical use of opioids and restoring patients to a healthier life.

In addition, new patient care models and improvements in the quality and quantity of treatment options are being encouraged through implementation of the Affordable Care Act. These new developments reveal the considerable potential for expanding the use of medication-assisted treatment as clinicians recognize their safety, efficacy, and cost-effectiveness.

APPENDIX A: MEMBERS OF THE CONSENSUS PANEL, STAFF, AND CONSULTANTS[§]

PANEL CHAIR

Charles P. O'Brien, M.D., Ph.D.
Kenneth E. Appel Professor of Psychiatry
University of Pennsylvania Treatment Research Center
Philadelphia, Pennsylvania

PANEL MEMBERS

Peter R. Cohen, M.D.
Medical Director
Maryland Alcohol & Drug Abuse Administration
Catonsville, Maryland

Sandra Comer, Ph.D.
Associate Professor of Clinical Neuroscience
Department of Psychiatry
Columbia College of Physicians & Surgeons
New York, New York

Marc J. Fishman, M.D.
Assistant Professor Department of Psychiatry
Johns Hopkins University School of Medicine,
and Medical Director
Maryland Treatment Centers
Baltimore, Maryland

Margaret Haney, Ph.D.
Professor of Clinical Neurobiology
Columbia University and
New York State Psychiatric Institute
New York, New York

Richard Hawks, Ph.D.
Consultant
National Institute on Drug Abuse
Washington, D.C.

Constance Horgan, Sc.D.
Associate Dean for Research and Director
Institute for Behavioral Health
Brandeis University
Heller School for Social Policy and Management
Waltham, Massachusetts

Reese T. Jones, M.D.
Professor of Psychiatry
University of California, San Francisco and Langley Porter
Psychiatric Institute
San Francisco, California

Herbert D. Kleber, M.D.
Professor of Psychiatry
Director, Division on Substance Abuse
Columbia University
New York, New York

Evgeny Krupitsky, M.D., Ph.D.
Professor and Chief
Laboratory of Clinical Psychopharmacology of
Addictions; St. Petersburg State Medical
University, and Chief, Department of Addictions
Bekhterev Research Psychoneurological Institute
St. Petersburg, Russia

Joseph G. Liberto, M.D.
Associate Professor of Psychiatry
University of Maryland School of Medicine
Baltimore, Maryland

Paolo Mannelli, M.D.
Associate Professor of Psychiatry
Duke University Medical Center
Chapel Hill, North Carolina

Tami L. Mark, Ph.D., M.B.A.
Senior Director
Analytic Consulting and Research Services
Truven Health Analytics
Washington, D.C.

Percy Menzies, M.Pharm.
President
Assisted Recovery Centers of America
St. Louis, Missouri

Edward Nunes, M.D.
Professor of Clinical Psychiatry
Columbia University and New York State
Psychiatric Institute
New York, New York

Patrick G. O'Connor, M.D., M.P.H.
Professor of Medicine and Chief,
General Internal Medicine
Yale School of Medicine
New Haven, Connecticut

George E. Woody, M.D.
Professor of Psychiatry
Veterans Administration Medical Center
Philadelphia, Pennsylvania

[§] Affiliations listed are positions held at the time of the consensus panel in July 2012.

Staff and Consultants**

HRSA STAFF

Rita Vandivort-Warren, M.S.W.
Office of Special Health Affairs
Health Resources and Services Administration
Rockville, Maryland

NIAAA STAFF

Raye Z. Litten, Ph.D.
Associate Director
Division of Treatment and Recovery Research
National Institute on Alcohol Abuse and Alcoholism/NIH
Rockville, Maryland

NIDA STAFF

Lori Ducharme, Ph.D.
Health Scientist Administrator
Division of Epidemiology, Services and Prevention Research
National Institute on Drug Abuse/NIH
Bethesda, Maryland

Ivan Montoya, M.D., M.P.H.
Deputy Director
Office of the DPMC Director
National Institute on Drug Abuse/NIH
Bethesda, Maryland

Betty Tai, Ph.D.
Director
Center for Clinical Trials Network
National Institute on Drug Abuse/NIH
Bethesda, Maryland

ONDCP STAFF

June S. Sivilli, M.A.
Chief, Treatment Branch
White House Office of National Drug Control Policy
Executive Office of the President
Washington, D.C.

Cecelia McNamara Spitznas, Ph.D.
White House Office of National Drug Control Policy
Executive Office of the President
Washington, D.C.

SAMHSA STAFF

Melinda Campopiano von Klimo, M.D.
Medical Officer
Center for Substance Abuse Treatment/SAMHSA
Rockville, Maryland

H. Westley Clark, M.D., J.D., M.P.H., CAS
Director
Center for Substance Abuse Treatment/SAMHSA
Rockville, Maryland

Peter Delany, Ph.D., LCSW-C
Acting Director
Center for Substance Abuse Treatment/SAMHSA
Rockville, Maryland

LCDR Brandon Johnson, M.B.A.
LCDR, U.S. Public Health Service Commissioned Corps
Public Health Advisor
Division of Pharmacologic Therapies
Center for Substance Abuse Treatment/SAMHSA
Rockville, Maryland

Erich Kleinschmidt, M.S.W.
CDR, Commissioned Corps
Division of Pharmacologic Therapies
Center for Substance Abuse Treatment/SAMHSA
Rockville, Maryland

Elinore McCance-Katz, M.D., Ph.D.
Chief Medical Officer
SAMHSA
Rockville, Maryland

Sandrine Pirard, M.D., Ph.D., M.P.H.
Medical Advisor
Division of Pharmacologic Therapies
Center for Substance Abuse Treatment/SAMHSA
Rockville, Maryland

CDR Alina Salvatore, R.Ph., M.S.
Public Health Advisor
Division of Pharmacologic Therapies
Center for Substance Abuse Treatment/SAMHSA
Rockville, Maryland

PROJECT CONSULTANTS

Anton C. Bizzell, M.D.
President
The Bizzell Group, LLC
Silver Spring, Maryland

Krystyna Isaacs, Ph.D.
Senior Researcher
JBS International, Inc.
North Bethesda, Maryland

Jane Carlisle Maxwell, Ph.D.
Senior Research Scientist
School of Social Work
University of Texas at Austin
Austin, Texas

Joseph Perpich, M.D., J.D.
Principal & Senior Medical Advisor
JBS International, Inc.
North Bethesda, Maryland

PROJECT DIRECTORS

Susan Hayashi, Ph.D.
Vice-President
JBS International, Inc.
North Bethesda, Maryland

Bonnie B. Wilford, M.S.
Director
Center for Health Services & Outcomes Research, and Senior Principal
JBS International, Inc.
North Bethesda, Maryland

** Affiliations listed are positions held at the time of the project work.

APPENDIX B: SOURCES OF INFORMATION

SAMHSA Publications and Web sites

National Registry of Evidence-based Programs and Practices
http://www.nrepp.samhsa.gov/Index.aspx

Treatment Improvement Protocol 45. *Detoxification and Substance Abuse Treatment*. HHS Publication No. (SMA) 08-4131
http://www.kap.samhsa.gov/products/manuals/tips/ pdf/TIP45.pdf

SAMHSA Treatment Locator
http://www.samhsa.gov/treatment/index.aspx

SAMHSA Advisory: *The Role of Biomarkers in the Treatment of Alcohol Use Disorders*, 2012 Revision
http://www.kap.samhsa.gov/products/manuals/advisory/pdfs/Advisory_Biomarkers_Revision.pdf

Coding for Screening and Brief Intervention Reimbursement
http://www.samhsa.gov/sbirt/coding-reimbursement

General Principles for the Use of Pharmacological Agents to Treat Individuals with Co-Occurring Mental and Substance Use Disorders
http://www.samhsa.gov/co-occurring/docs/Pharm_Principles_508.pdf

Opioid Overdose Toolkit
http://www.store.samhsa.gov/product/Opioid-Overdose-Prevention-Toolkit/SMA13-4742

NIDA Publications and Web Sites

Comorbidity: Addiction and Other Mental Illness (Research Report Series; Publication Number 10-5771). Rockville, MD: National Institutes of Health, 2010.

Principles of Drug Addiction Treatment: A Research-Based Guide, Third Edition. Rockville, MD: National Institutes of Health, 2012.

Mentoring Network

Physician Clinical Support System for Medication-Assisted Treatment
http://www.pcssmat.org

Information About Mutual Support Groups

Narcotics Anonymous (NA)
http://www.na.org

Dual Recovery Anonymous (for patients with co-occurring psychiatric disorders)
http://www.draonline.org

Self-Management and Recovery Training
http://www.smartrecovery.org

Web-Based Courses

American Society of Addiction Medicine (ASAM) *SBIRT Core Training Program*
http://www.sbirttraining.com/

ASAM *e-Live Learning Center*
http://www.softconference.com/asam/default.asp

ASAM *From Assessment to Service Planning and Level of Care Course*
http://www.changecompanies.net/asamcriteria/elearning.php

Other Web Sites, Articles, and Texts

Alliance of States with Prescription Monitoring Programs
http://www.pmpalliance.org/

U.S. Department of Health and Human Services, Centers for Medicare & Medicaid Services. *Fact Sheet: Substance (Other Than Tobacco) Abuse Structured Assessment and Brief Intervention (SBIRT) Services*.
http://www.prescribetoprevent.files.wordpress.com/2012/01/sbirt-guidance-document.pdf

U.S. Departments of Veterans Affairs and Defense. *VA/DoD Clinical Practice Guideline for Management of Substance Use Disorders in the Primary Care Setting.* http://www.healthquality.va.gov/sud/sud_fulltext.pdf

The ASAM Criteria, Third Edition (PPC-3), 2013 http://www.asam.org/publications/patient-placement-criteria

British Association for Psychopharmacology. *Evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: Recommendations from BAP*. London: June 2012. http://www.bap.org.uk/pdfs/BAPaddictionEBG_2012.pdf

Principles of Addiction Medicine, Fifth Edition, 2014 http://www.asam.org/publications/principles-of-addiction-medicine

Principles of Addiction Medicine: The Essentials http://www.asam.org/publications/principles-the-essentials

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), 2013 http://www.psych.org/

APPENDIX C: ACKNOWLEDGMENTS

CDR Alina Salvatore, R.Ph., M.S., and LCDR Brandon T. Johnson, M.B.A., of the Division of Pharmacologic Therapies, Center for Substance Abuse Treatment (CSAT), Substance Abuse and Mental Health Services Administration (SAMHSA), U.S. Department of Health and Human Services (HHS), served as the Contracting Officer's Representatives for this project. Robert A. Lubran, M.S., M.P.A., Director of SAMHSA's Division of Pharmacologic Therapies, provided valuable guidance, as did Elinore McCance-Katz, M.D., Ph.D., Sandrine Pirard, M.D., Melinda Campopiano von Klimo, M.D., Erich Kleinschmidt, M.S.W., and other experts at SAMHSA, the National Institute on Drug Abuse (NIDA), other federal agencies, and private-sector organizations.

Members of the Consensus Panel on New Pharmacotherapies for Opioid Use Disorders and Related Comorbidities graciously agreed to serve as peer reviewers of the document. Their many contributions are acknowledged with gratitude.

Special appreciation is extended to panel chair Charles P. O'Brien, M.D., Ph.D., and to Ivan Montoya, M.D., M.P.H., Lori J. Ducharme, Ph.D., and Betty Tai, Ph.D., of NIDA.

Susan W. Hayashi, Ph.D. and Bonnie B. Wilford, M.S., served as Project Directors, with valuable assistance from Joseph Perpich, M.D., J.D., Krystyna Isaacs, Ph.D., Gwen Solan Littman, M.D., Thomas G. Durham, Ph.D., Jeffrey Vender, M.L.I.S., Leotta Britton, and Valerie L. Vivian, M.B.A., of JBS International. Jane C. Maxwell, Ph.D., of the University of Texas at Austin, was consulting epidemiologist.

REFERENCES

[1] Substance Abuse and Mental Health Services Administration (SAMHSA). *Treatment Advisory: An Introduction to Extended-Release Injectable Naltrexone for the Treatment of People With Opioid Dependence.* (Volume 11, Issue 1 [SMA] 12-4682). Rockville, MD: Office of Applied Studies, SAMHSA, 2012.

[2] Substance Abuse and Mental Health Services Administration (SAMHSA). Center for Behavioral Health Statistics and Quality. (2014). *Results from the 2013 National Survey on Drug Use and Health: Summary of national findings* (HHS Publication No. 14–4863, NSDUH Series H–48). Rockville MD: Substance Abuse and Mental Health Services Administration.

[3] Arfken CL, Johanson CE, diMenza S, et al. Expanding treatment capacity for opioid dependence with buprenorphine: National surveys of physicians. *J Subst Abuse Treat*. 2010 Sep;39(2):96–104.

[4] Gunderson EW, Fiellin DA. Office-based maintenance treatment of opioid dependence: How does it compare with traditional approaches? *CNS Drugs.* 2008;22(2):99–111.

[5] Substance Abuse and Mental Health Services Administration (SAMHSA) and the National Institute on Drug Abuse. *Report of the Consensus Panel on New Pharmacotherapies for Opioid Use Disorders and Related Comorbidities* (Report of the Meeting of July 17–18, 2012). Rockville, MD: SAMHSA, October 2012.

[6] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition. Washington, DC: American Psychiatric Publishing, Inc., 2013.

[7] Barry DT, Irwin KS, Jones ES, et al. Integrating buprenorphine treatment into office-based practice: A qualitative study. *J Gen Intern Med*. 2009 Feb; 24(2):218–225.

[8] Bruce RD. Medical interventions for addictions in the primary care setting. *Topics HIV Med.* 2010 Feb–Mar;18(1):8–12.

[9] Fiellin DA, Moore BA, Sullivan LE, et al. Long-term treatment with buprenorphine/naloxone in primary care: Results at 2-5 years. *Am J Addict*. 2008 Mar–Apr;17(2):116–120.

[10] Finch JW, Kamien JB, Amass L. Two-year experience with buprenorphine/naloxone (Suboxone) for maintenance treatment of opioid dependence within a private practice setting. *J Addict Med.* 2007 Jun;1(2):104–110.

[11] Jones ES, Moore BA, Sindelar JL, et al. Cost analysis of clinic and office-based treatment of opioid dependence: Results with methadone and buprenorphine in clinically stable patients. *Drug Alcohol Depend*. 2009 Jan 1;99(1-3):132–1340.

[12] Magura S, Lee SJ, Salsitz EA, et al. Outcomes of buprenorphine maintenance in office-based practice. *J Addict Dis.* 2007;26(2):13–23.

[13] Sullivan LE, Fiellin DA. Narrative review: Buprenorphine for opioid-dependent patients in office practice. *Ann Intern Med*. 2008 May 6;148(9):662–670. Review.

[14] Torrington M, Domier CP, Hillhouse M, et al. Buprenorphine 101: Treating opioid dependence with buprenorphine in an office-based setting. *J Addict Dis.* 2007; 26(3):93–99.

[15] Walley AY, Alperen JK, Cheng DM, et al. Office-based management of opioid dependence with buprenorphine: Clinical practices and barriers. *J Gen Intern Med.* 2008 Sep;23(9):1393–1398.

[16] Levounis P. Patient assessment. In JA Renner, Jr. & P Levounis, eds., *Handbook of Office-Based Buprenorphine Treatment of Opioid Dependence*. Washington, DC: American Psychiatric Publishing, Inc., 2011.

[17] Federation of State Medical Boards of the United States (FSMB). *Model Policy on the Use of Opioid Analgesics in the Treatment of Chronic Pain.* Dallas, TX: The Federation, July 2013.

[18] Breen CL, Harris SJ, Lintzeris N, et al. Cessation of methadone maintenance treatment using buprenorphine: Transfer from methadone to buprenorphine and subsequent buprenorphine reductions. *Drug Alcohol Depend*. 2003 Jul 20;71(1):49–55.

[19] Kraus ML, Alford DP, Kotz MM, et al. Statement of the American Society of Addiction Medicine Consensus Panel on the Use of Buprenorphine in Office-Based Treatment of Opioid Addiction. *J Addict Med*. 2011 Dec;5(4):254–263.

[20] State Prescription Drug Monitoring Programs. Department of Justice, Drug Enforcement Agency, Office of Diversion Control Web Site. http://www.deadiversion.usdoj.gov/ Updated October 2011. Accessed August 15, 2014.

[21] World Health Organization (WHO). *Guidelines for the Psychologically Assisted Pharmacological Treatment of Opioid Dependence*. Geneva, Switzerland: WHO, 2009.

[22] Saitz R. Medical and surgical complications of addiction. In RK Ries, DA Fiellin, SC Miller, R Saitz, eds., *Principles of Addiction Medicine*, Fourth Edition. Philadelphia, PA: Lippincott, Williams & Wilkins, 2009.

[23] Gourlay DL, Heit HA, Caplan YH. *Urine Drug Testing in Clinical Practice: The Art and Science of Patient Care*. 2010. Sacramento, CA: California Society of Family Physicians, 2010.

[24] National Institute on Drug Abuse (NIDA). *Principles of Drug Addiction Treatment: A Research-Based Guide*, Third Edition. Rockville, MD: National Institutes of Health, 2012.

[25] McNicholas L. Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction. *A Tool for Buprenorphine Care.* 2008 May;1(12):12–20.

[26] Center for Substance Abuse Treatment (CSAT). *Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs* (Treatment Improvement Protocol 43). HHS Publication No. (SMA) 08-4214. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2008.

[27] Vivitrol (extended release naltrexone) prescription drug label. U.S. National Library of Medicine Web site. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=74696d65-6973-6275-7461-77696e646f77 Published July 2013. Accessed October 14, 2014.

[28] Alkermes, Inc. Medication guide. Revised November 2010, VIV993B). Waltham, MA: Alkermes, 2010. [Accessed at http://www.vivitrol.com/Content/pdf/medication_guide.pdf]

[29] Food and Drug Administration (FDA). Vivitrol (naltrexone for extended-release injectable suspension) FDA Psychopharmacologic Drugs Advisory Committee Meeting [briefing document/background package]. NDA 21-897. Rockville, MD: FDA, 2010 [Accessed at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommit%20%20tee/UCM225664.pdf

[30] Center for Substance Abuse Treatment. *Quick Guide for Clinicians Based on TIP 43.* HHS Publication No. (SMA) 05-4107. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2005a. [Accessed at http://www.atforum.com/pdf/QGC_43-2.pdf]

[31] Food and Drug Administration (FDA). *Methadose™ Oral Concentrate (methadone hydrochloride oral concentrate USP) and Methadose™ Sugar-Free Oral Concentrate (methadone hydrochloride oral concentrate USP) dye-free, sugar-free, unflavored.* Rockville, MD: FDA, 2007. [Accessed at http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/017116s021lbl.pdf]

[32] Johansson BA, Berglund M, Lindgren A. Efficacy of maintenance treatment with naltrexone for opioid dependence: A meta-analytical review. *Addiction* 2006;101:491–503.

[33] Kaltenbach K, Silverman N, Wapner R. Methadone maintenance during pregnancy. In: *State Methadone Treatment Guidelines.* Treatment Improvement Protocol (TIP) Series 1. DHHS Publication No. (SMA) 02-3624. Rockville, MD: Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, 1993.

[34] Lobmaier P, Kornor H, Kunoe N, et al. Sustained-release naltrexone for opioid dependence. *Cochrane Database Syst Rev*. 2008; CD006140.

[35] Lobmaier PP, Kunoe N, Gossop M, et al. Naltrexone depot formulations for opioid and alcohol dependence: A systematic review. *CNS Neurosci Ther.* 2011 Dec;17(6):629–636.

[36] Mallinckrodt Inc. Methadose dispersible tablets prescribing information. Hazelwood, MO: Mallinckrodt, 2013. [Accessed at http://www.mallinckrodt.com/Generics/Package_Inserts_Medication_Guides.aspx]

[37] Mannelli P. Once-monthly extended-release naltrexone injections improve opioid abstinence over 24 weeks compared with placebo. *Evid Based Ment Health.* 2011 Nov;14(4):106.

[38] Merlo LJ, Greene WM, Pomp R. Mandatory naltrexone treatment prevents relapse among opiate-dependent anesthesiologists returning to practice. *J Addict Med.* 2011 Dec;5(4):279–283.

[39] O'Brien CP. Toward a rational selection of treatment for addiction. *Curr Psychiatry Rep.* 2007 Dec;9(6):441–442.

[40] O'Brien C, Kampman KM. Antagonists of opioids (Chapter 22). In M Galanter & HD Kleber, eds., *APA Textbook of Substance Abuse Treatment*. Washington, DC: American Psychiatric Publishing, Inc., 2008.

[41] Office of National Drug Control Policy. Medication-assisted treatment of opioid addiction. *Health Care Brief.* 2012 September. [Accessed at http://www.whitehouse.gov/sites/default/files/ondcp/recovery/medication_assisted_treatment_9-21-20121.pdf]

[42] Reckitt Benckiser Pharmaceuticals Inc. *Evolving Treatment Empowering Patients: A Physician's Guide to the Latest Innovation in Opioid-Dependence Treatment*. Richmond, VA: Reckitt Benckiser Pharmaceuticals, 2010

[43] Saber-Tehrani AS, Bruce RD, Altice FL. Pharmacokinetic drug interactions and adverse consequences between psychotropic medications and pharmacotherapy for the treatment of opioid dependence. *Am J Drug Alcohol Abuse* 2011; 37(1):1–11.

[44] Sullivan M, Rothenberg J, Vosburg S et al. Predictors of retention in naltrexone maintenance for opioid dependence: analysis of a stage I trial*. Am J Addict.* 2006 Mar-Apr:15(2), 150-159.

[45]Mannelli P, Peindl KS, Wu LT. Pharmacological enhancement of naltrexone treatment for opioid dependence: A review. *Subst Abuse Rehabil.* 2011 June;2:113–123.

[46] Food and Drug Administration (FDA). *Information for Healthcare Professionals: Naltrexone Injection Site Reactions (Naltrexone for Extended-Release Injectable Suspension, marketed as Vivitrol).* Rockville, MD: FDA, August 2008.

[47]Comer SD, Sullivan MA, Yu E, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence: A randomized, placebo controlled trial. *Arch Gen Psychiatry* 2006 Feb; 63(2):210–218.

[48] Kranzler HR, Wesson DR, Billot L, et al., for the Drug Abuse Sciences Naltrexone Depot Study Group. Naltrexone depot for treatment of alcohol dependence: A multicenter, randomized, placebo-controlled clinical trial. *Alcohol Clin Exp Res* 2004; 28(7):1051–1059.

[49] Garbutt JC, Kranzler HR, O'Malley SS, et al., for the Vivitrol Study Group. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: A randomized controlled trial. *JAMA* 2005;293:1617–1625.

[50] Krupitsky EM, Nunes EV, Ling W, et al. Injectable extended-release naltrexone for opioid dependence: A double-blind, placebo-controlled, multicentre randomised trial. *Lancet* 2011; 377:1506–1513.

[51] Sigmon SC, Bisaga A, Nunes EV, et al. Opioid detoxification and naltrexone induction strategies: Recommendations for clinical practice. *Am J Drug Alcohol Abuse* 2012; 38(3):187–199.;

[52] National Institute on Drug Abuse. *Principles of Drug Addiction Treatment: A Research-Based Guide*, Second Edition*.* Rockville, MD: National Institutes of Health, 2009.

[53] Fishman MJ, Winstanley EL, Curran E, et al. Treatment of opioid dependence in adolescents and young adults with extended release naltrexone: Preliminary case-series and feasibility. *Addiction* 2010 Sep;105(9):1669–1676.

[54] Lingford-Hughes AR, Welch S, Peters L, et al. Evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: Recommendations from BAP (British Association for Psychopharmacology). *J Psychopharm.* 2012 Jun. 25.

[55] Fishman MJ, Mee-Lee D, Shulman GD, et al. *Supplement on Pharmacotherapies for Alcohol Use Disorders to the ASAM Patient Placement Criteria.* Philadelphia, PA: Lippincott, Williams & Wilkins, 2010.

[56] Seal KH, Shi Y, Cohen G, et al. Association of mental health disorders with prescription opioids and high risk opioid use in U.S. veterans of Iraq and Afghanistan. *JAMA.* 2012;307(9):940–947.

[57] Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-IIIR psychiatric disorders in the United States. *Arch Gen Psychiatry.* 1994;51:8–19.

[58] National Institute on Drug Abuse. *Comorbidity: Addiction and Other Mental Illness* (Research Report Series; Publication Number 10-5771). Rockville, MD: National Institutes of Health, 2010.

[59] Robins LN, Locke BZ, Regier D. An overview of psychiatric disorders in America. In LN Robins, DA Regier, eds., *Psychiatric Disorders in America: The Epidemiologic Catchment Area Study*. New York, NY: Free Press, 1991, pp. 328–366.

[60] Coviello DM, Cornish JW, Lynch KG, et al. A multisite pilot study of extended-release injectable naltrexone treatment for previously opioid-dependent parolees and probationers. *Subst Abuse* 2012;33(1):48–59.

[61] Samet J, Friedmann P, Saitz R. Benefits of linking primary medical care and substance abuse services: Patient, clinician, and societal perspectives. *Arch Int Med*. January 8, 2001;161(1):85–91.

[62] Center for Substance Abuse Treatment. *Substance Abuse Treatment for Persons With Co-Occurring Disorders* (Treatment Improvement Protocol 42). HHS Publication No. (SMA) 05-3992. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2005b.

[63] Fleming MF, Davis J, Passik SD. Reported lifetime aberrant drug-taking behaviors are predictive of current substance use and mental health problems in primary care patients. *Pain Med*. 2008 November; 9(8): 1098–1106.

[64] Department of Veterans Affairs & Department of Defense*. VA/DoD Clinical Practice Guideline for Management of Substance Use Disorders (SUD).* Washington, DC. Veterans Health Administration, Department of Veterans Affairs and Health Affairs, Department of Defense, 2009.

[65] McCance-Katz EF, Sullivan LS, Nallani S: Drug interactions of clinical importance between the opioids, methadone and buprenorphine, and frequently prescribed medications: A review. Am J Addictions, 19: 4–16, 2010.

[66] Cooper Z, Haney M. Opioid antagonism enhances marijuana's effects in heavy marijuana smokers. *Psychopharmacology* 2010; 211(2), 141–148.

[67] Swendsen J, Burstein M, Case B, et al. Use and abuse of alcohol and illicit drugs in U.S. adolescents: Results of the National Comorbidity Survey—Adolescent Supplement. *Arch Gen Psychiatry* 2012 Apr;69(4):390–398.

[68] Faird WO, Dunlop SA, Tait RJ, et al. The effects of maternally administered methadone, buprenorphine, and naltrexone on offspring: Review of human and animal data. *Curr Neurophamacol.* 2008 Jun;6(2)125–150.

[69] Meyer M, Paranya G, Keefer-Norris A, et al. Intrapartum and postpartum analgesia for women maintained on buprenorphine during pregnancy. *Eur J Pain*. 2010 Oct;14(9):939–943.

[70] Unger A, Metz V, Fischer G. Opioid dependent and pregnant: What are the best options for mothers and neonates? *Obstet Gynecol Int.* 2012. [Epub]

[71] Jones HE, Chisolm MS, Jansson LM, et al. Naltrexone in the treatment of opioid-dependent pregnant women: The case for a considered and measured approach to research. *Addiction* 2013 Feb;108(2):255–56.

[72] Moy I, Crome P, Crome I, et al. Systematic and narrative review of treatment for older people with substance problems. *Eur Geriatr Med.* 2011;2:212–236.

[73] DeFulio A, Everly JJ, Leoutsakos JM, et al. Employment-based reinforcement of adherence to an FDA-approved extended release formulation of naltrexone in opioid-dependent adults: A randomized controlled trial. *Drug Alcohol Depend.* 2012 Jan 1;120(1–3):48–54.

[74] Tai B, Blaine J, for the Treatment Workgroup of the National Institute on Drug Abuse (NIDA). Naltrexone: An antagonist therapy for heroin addiction. *NIDA Meeting Summary, 12–13 November 1997*. Rockville, MD: National Institutes of Health, 1998.

[75] Oreskovich MR, Caldeiro H. Anesthesiologists recovering from chemical dependency: Can they safely return to the operating room? *Mayo Clin. Proc.* 2001;84:576–580.

[76] Friedmann PD, Hoskinson R, Gordon M, et al., for the MAT Working Group of CJ-DATS. Medication-assisted treatment in criminal justice agencies affiliated with the criminal justice-drug abuse treatment studies (CJ-DATS): Availability, barriers, and intentions. *Subst Abuse* 2012;33(1):9–18.

[77] Amato L, Minozzi S, Davoli M, et al. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *Cochrane Database Syst Rev*. 2008;4:CD005031.

[78] Krupitsky EM, Blokhina EA. Long-acting depot formulations of naltrexone for heroin dependence: A review. *Curr Opin Psychiatry* 2010;23(3):210–214.

[79] Lobmaier P, Gossop M, Waal H, et al. The pharmacological treatment of opioid addiction: A clinical perspective. *Eur J Clin Pharmacol.* 2010;66:537–545.

[80] Tetrault JM, Fiellin DA. Current and potential pharmacological treatment options for maintenance therapy in opioid-dependent individuals. *Drugs* 2012 Jan 22; 72(2):217–228.

[81] Jones HE. Practical Considerations for the Clinical Use of Buprenorphine. *Science and Practice Perspectives*. 2004 Aug;2(2):4-20.

[82] SAMHSA/CSAT Treatment Improvement Protocols: Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs (2005), Ch. 13: Medication-Assisted Treatment for Opioid Addiction During Pregnancy. http://www.ncbi.nlm.nih.gov/books/NBK64148/

[83]Food and Drug Administration (FDA). *Methadose™ Sugar-Free Oral Concentrate (methadone hydrochloride oral concentrate USP) Dye-Free, Sugar-Free, Unflavored*. Rockville, MD: Author, 2007. [Accessed at http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/017116s021lbl.pdf

[84] Gibson AE, Degenhart LJ. Mortality related to pharmacotherapies for opioid dependence: A comparative analysis of coronial records. *Drug Alc Rev* 2007 Jul;26:405–410.

[85] Helm S, Trescot AM, Colson J, et al. Opioid antagonists, partial agonists, and agonists/antagonists: The role of office-based detoxification. *Pain Physician* 2008;11(2):225–235. Review.

[86] Center for Substance Abuse Treatment. Protracted Withdrawal. *Substance Abuse Treatment Advisory* 2010; 9(1).

[87] Bell J, Kimber J, Lintzeris N, et al. *National Drug Strategy: Clinical Guidelines for the Use of Naltrexone in the Management of Opioid Dependence*. Canberra, Australia: Department of Health and Ageing, 2003.

[88] Centers for Disease Control and Prevention. Deaths and severe adverse events associated with anesthesia-assisted rapid opioid detoxification—New York City, 2012. *Morbid Mortal Weekly Rep*. 2013 Sep. 26.

[89] O'Brien CP. Anticraving medications for relapse prevention: A possible new class of psychoactive medications. *Am J Psychiatry* 2005;162(8):1423–1431.

[90] Kleber HD. Pharmacologic treatments for opioid dependence: Detoxification and maintenance options. *Dialogues Clin Neurosci.* 2007;9(4):455–70. Review.

[91] Center for Substance Abuse Treatment. Naltrexone: Extended- release injectable suspension for treatment of alcoholism dependence. *Substance Abuse Treatment Advisory* 2007 Spring;6(1):1–6.

[92] National Institute for Health and Clinical Excellence, National Health Service. *Naltrexone for the Management of Opioid Addiction* (Technology Appraisal Guidance No. 115). London, UK: National Institute for Health and Clinical Excellence, 2010.

[93] Bloodworth D. Opioids in the treatment of chronic pain: Legal framework and therapeutic indications and limitations. *Physical Medicine and Rehabilitation Clinics of North America.* 2006;17:355–379.

[94] Wilford BB, DuPont RL. Prescription drug abuse. In A Wertheimer & T Fulda, eds., *A Textbook on Pharmaceutical Policy*. Binghamton, NY: The Haworth Press, 2007.

[95] Stotts AL, Dodrill CL, Kosten TR. Opioid dependence treatment: Options in pharmacotherapy. *Expert Opin Pharmacother.* 2009 Aug; 10(11):1727–1740.

[96] Zweben A, Pettinati HM, Weiss RD, et al. Relationship between medication adherence and treatment outcomes: The COMBINE study. *Alcohol Clin Exp Res.* 2008 Sep; 32(9):1661–1669.

[97] Dimeff LA, Marlatt GA. *Relapse prevention*. In R Hester, W Miller, eds., *Handbook of Alcoholism Treatment Approaches,* 2nd Edition. Boston, MA: Allyn & Bacon, 1995, pp. 176–194.

[98] Marlatt G, Gordon JR, eds. *Relapse Prevention: Maintenance Strategies in the Treatment of Addictive Behaviors.* New York, NY: Guilford Press, 1985.

[99] Institute for Research, Education and Training in Addiction. *Best Practices in the Use of Buprenorphine.* Final Expert Panel Report. Pittsburgh, PA: Community Care Behavioral Health Organizations, October 18, 2011.

[100] Stephenson DK, for the CSAM Committee on Treatment of Opioid Dependence. *Draft Guidelines for Physicians Working in California Opioid Treatment Programs*. San Francisco, CA: California Society of Addiction Medicine, 2008.

[101] Digiusto E, Shakeshaft A, Ritter A, et al., for the NEPOD Research Group. Serious adverse events in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD). *Addiction* 2004;99(4):450–460.

[102] Substance Abuse and Mental Health Services Administration (SAMHSA). *Opioid Overdose Toolkit*. Rockville, MD: SAMHSA, 2014.

Substance Abuse and Mental Health Services Administration
SAMHSA
www.samhsa.gov • 1-877-SAMHSA-7 (1-877-726-4727)

HHS Publication No. SMA14-4892R
First Printed 2015