Meeting the Need

Doing more to help address the crisis of opioid and alcohol dependence

Treating Opioid Dependence: What More Can Be Done to Help?

ISSUE 2: TREATMENT OPTIONS AND BARRIERS

Government statistics indicate that our country's opioid epidemic continues to worsen (see Issue 1).[1,2] Yet, available treatments for patients remain underutilized.[3] To help address our opioid crisis, clinicians must ensure that patients seeking help for opioid dependence have access to all appropriate therapies.

This newsletter will briefly review available treatment options for patients with opioid dependence, with a focus on an antagonist medication. Then it will explore treatment barriers, particularly those associated with the use of medication-assisted treatment (MAT), and how some might be addressed.

It is important to note that "substance dependence" as defined in the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) partially served as the basis for the U.S. Food and Drug Administration's approval of most available MATs.[4-10] The fifth edition of the manual updated the diagnostic criteria for opioid disorders. The category "substance dependence" was replaced with an overarching category of "substance use disorders," with the specific substance defining each specific disorder (e.g., opioid use disorder).[11] The former term is used in this newsletter to be consistent with the approved indication for numerous MAT options.

Medically Managed Withdrawal (Detoxification): a Potential First Step

The goal of medically managed withdrawal (MMW), or detoxification, is to safely manage the acute physical symptoms of withdrawal that are associated with stopping opioid use.[12] According to the National Institute on Drug Abuse (NIDA), MMW can be the first step in the treatment of opioid addiction but does not typically produce the changes necessary for recovery.[12] MMW may occur in a variety of different treatment settings.[13]

MMW (with or without medication) does not address the psychological, social, and behavioral problems associated with dependence.[12,14] Only 15% of people who are admitted to an MMW program through an emergency department and then discharged go on to receive additional treatment.[13] Few opioid-dependent individuals can remain abstinent without additional help

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immediately after MMW, and psychosocial interventions alone may not be enough to prevent relapse.[14,15]

Psychosocial Interventions

Psychosocial interventions such as counseling or behavioral therapy are an important part of any opioid-dependence treatment plan, including MAT approaches.[6-8,10,16] According to NIDA, behavioral approaches help engage people in opioid-dependence treatment, provide incentives for them to remain abstinent, help modify their attitudes and behaviors related to opioid use, and help increase their life skills to handle stressful circumstances and environmental cues that may trigger intense craving for opioids and prompt another cycle of compulsive abuse.[12]

In 2016, Dugosh and colleagues published a systematic analysis of studies of psychosocial interventions used in conjunction with MAT approaches.[17] The most commonly studied interventions were contingency management and cognitive behavioral therapy.[17] Psychosocial interventions in combination with MAT were found to be effective in treating opioid dependence. However, the extent of the benefit was variable due to different study types, measured outcomes, medications used, and interventions performed.[17] Further research is necessary to elucidate the optimal types of psychosocial interventions needed to meet individual patient needs.

Such a dual "psychosocial intervention plus medication" approach to treatment is consistent with our knowledge of opioid dependence and the 2 primarily affected brain regions (see **Issue 1**): the cortex (responsible for decision-making, thinking, reasoning, and planning) and the limbic system (responsible for basic drives, urges, rewards, and pleasure).[18]

Medication-Assisted Treatment

MAT has been proven effective in opioid-dependent patients, yet most patients do not receive it.[3] In fact, according to a 2015 analysis based on data from the National Survey of Drug Use and Health (NSDUH), only about 20% of Americans with an opioid use disorder received any kind of treatment from 2009 to 2013.[19] (The NSDUH does not independently track the use of MAT.[19]) The goals for opioid use disorder treatment include treatment retention, opioid use reduction or abstinence, and reduction in the frequency and severity of opioid use episodes.[20]

Broadly, there are 3 classes of MAT options available to help patients with opioid dependence, classified by their activity at mu opioid receptors: full agonist, partial agonist, and antagonist therapy.[21] According to practice guidelines from the American Society of Addiction Medicine (ASAM), when selecting treatment for an individual patient, the prescriber should consider patient preference, treatment history, and treatment setting.[16] Access and availability also may be important considerations.[22]

As stated earlier, psychosocial intervention is an important part of any treatment plan that includes MAT.[6-8,10,16]

Full agonist therapy

Full opioid agonist medications used for MAT (e.g., methadone) bind to mu opioid receptors and fully activate them.[23] These medications are administered daily, in oral form, and are provided only within the context of a certified opioid treatment program.[23] Full opioid agonists are Schedule II controlled substances.[23,24] MMW is not required prior to initiating full-agonist treatment, but may be required if a patient decides to discontinue treatment.[23,25]

> *Medication-assisted treatment has been proven effective in opioid-dependent patients, yet most patients do not receive it.*[3]

Partial agonist therapy

Partial agonists (e.g., buprenorphine) have a pharmacologic profile different from that of full agonists. Partial agonists produce a less-than-maximal or partial agonist effect at the mu opioid receptor and an antagonistic effect at the kappa opioid receptor.[20]

This type of medication is available in multiple dosage forms.[6-9,26] Most forms can be taken by the patient at home after being initially provided by a licensed healthcare provider; however, the subdermal implant form must always be administered by a licensed healthcare provider.[6-9] Partial agonists are Schedule III controlled substances.[6,24]

MMW is not required prior to initiating partial-agonist treatment.[6,8] However, if patients decide to stop treatment with a partial agonist, MMW may be required.[6]

Antagonist therapy

Opioid antagonist medications used for MAT (e.g., oral or extended-release, injectable naltrexone) bind to mu opioid receptors in the brain, blocking the receptor from opioid agonist drugs.[10,12,27] Antagonist agents do not activate the opioid receptor, so there is no excessive stimulation of the dopamine reward system. Although some opioid antagonists, such as naloxone, are used for rapid reversal of opioid agonist effects (e.g., respiratory depression) in overdose settings, the antagonists used for MAT are longer-acting and are given along with psychosocial interventions to help prevent relapse to opioid dependence after MMW.[10,12] It is critical that patients are opioid free for a minimum of 7 to 10 days before beginning antagonist therapy, or precipitated opioid withdrawal can result.[10,27] Patients transitioning from full or partial agonists may be vulnerable to precipitation of withdrawal symptoms for as long as 2 weeks.

Patients taking opioid antagonist medication do not experience a high, and there is no known abuse potential.[27] Also, if patients cease treatment, they will not experience withdrawal symptoms.

The **Table** on page 3 summarizes some of the properties of full agonist, partial agonist, and antagonist medications used to treat opioid-dependent patients. **No comparisons of safety or efficacy, nor any treatment decisions, should be made based on this information.**

Patients taking opioid antagonist medication do not experience a high, and there is no known abuse potential.[27]

Overcoming Barriers to the Use of MAT

As noted earlier, available MAT options for patients dependent on opioids remain underutilized.[3] This section will review a few of the known potential barriers to MAT, as well as possible ways to address some of these barriers. The goal is to help ensure that MAT is available to all appropriate patients whom it might benefit.

Practice-related barriers

A variety of barriers to MAT utilization have been reported by clinicians. These include concerns about treating patients struggling with addiction; financial barriers such as poor reimbursement; a lack of institutional support for the use of MAT; lack of access to supporting specialty physicians or psychosocial resources for patients; time constraints; lack of confidence or training in providing MAT; resistance from practice partners; and restrictions/regulations concerning the use of MAT therapies.[32-36]

Cited approaches to help address some of these barriers include expanding provider education and increasing provider access to specialists to consult on patient management and the implementation of MAT in practice.[32,36] It should also be noted that regulations and training associated with prescribing MAT are highly dependent on the type of MAT therapy. For example, the use of nonscheduled opioid antagonist therapy is not associated with any special regulatory or training requirements.

Insurance coverage and restrictions

To assess the extent of patient access to MAT, the American Society of Addiction Medicine (ASAM) commissioned surveys of 50 state Medicaid programs and 30 private insurers.[22] The findings from the Medicaid survey indicated that all states covered at least 1 approved MAT option, but that many barriers to access existed.[22] These barriers included lack of coverage of all approved medications, limits on treatment duration or dosage, prior-authorization requirements, minimal coverage of counseling, the use of step therapy protocols, and limits on who can prescribe.[22]

The findings from the commercial-insurer survey indicated that most plans covered at least 1 MAT option but that access was limited by utilization management protocols—for example, prior authorization, quantity/dosage limits, and step therapy mandates.[22]

Table. Overview of MAT Options for Opioid Dependence.[6-10,12,23-31]

	Full Agonist Therapy	Partial Agonist Therapy	Antagonist Therapy
Binds to mu opioid receptor	YES	YES	YES
Activates mu opioid receptor to release dopamine	YES	YES but not to the extent of a full agonist	NO
Administration	Daily oral concentration	Daily sublingual film, sublingual tablet, buccal film, or 6-month subdermal implant	Daily oral medication or monthly intramuscular injection
Setting	Provided at certified opioid treatment program settings	Sublingual film, sublingual tablet, or buccal film can be initially provided in a physician's office then as a take-home medication. The 6-month subdermal implant requires HCP administration.	Daily oral can be provided as take-home medication. Monthly injection requires HCP administration.
DEA schedule	Schedule II controlled substance	Schedule III controlled substance	Not scheduled
Requires MMW	NO	NO	YES
Requires counseling	YES	YES	YES

DEA, Drug Enforcement Administration; HCP, healthcare provider; MMW, medically managed withdrawal.

This chart is not intended to make any product comparisons. No comparisons of safety or efficacy of any products are to be made.

The use of nonscheduled opioid antagonist therapy is not associated with any special regulatory or training requirements.

To help address these access barriers, ASAM underscores the importance of educating all stakeholders to raise awareness of the efficacy of available MAT options.[22]

Patient-related barriers

Reported patient-related barriers to MAT use include geographic access to treatment facilities and/or prescribing clinicians, as well as preconceptions or misconceptions about MAT—all of which can influence patients' views of MAT options.[35,37] Taking a patient-centered approach to MAT that includes individualization of therapy according to patient characteristics, needs, and preferences may help.[38]

Additionally, some patient-related barriers may be addressed through increased encouragement, support, and education of patients and caregivers by clinician staff.[37,39] With respect to education, information aimed at addressing patient and caregiver misconceptions may be particularly valuable.

Conclusions

There is no single solution to our country's crisis of opioid misuse and abuse. Fortunately, for patients seeking help for opioid dependence, treatment with psychosocial interventions and MAT may help make a difference.[3,10] Barriers to MAT use are varied, and some are treatment specific.[32-35,37,40] Addressing these barriers can help support patients on their challenging recovery journey.

Please refer to Issues 1 and 3 in this newsletter series for more information about opioid dependence as well as an antagonist treatment option. Visit MeetingTheNeed.CurrentPsychiatry.com.

References

1. Center for Behavioral Health Statistics and Quality. (2017). *2016 National Survey on Drug Use and Health: Detailed Tables*. Substance Abuse and Mental Health Services Administration, Rockville, MD. **2.** Centers for Disease Control and Prevention (CDC). Provisional counts of drug overdose deaths, as of 8/6/2017. https://www.cdc.gov/nchs/data/health_policy/monthly-drug-overdose-death-estimates.pdf. Accessed October 13, 2017. **3.** Department of Health and Human Services. *The Opioid Epidemic: By the Numbers*. https://www.hhs.gov/sites/default/files/Factsheet-opioids-061516.pdf. Updated June 2016. Accessed May 17, 2017. **4.** *Diagnostic and Statistical Manual of Mental Disorders. 4th ed.* Text Revision. Washington, DC: American Psychiatric Association; 2000. **5.** Subutex (buprenorphine) [package insert]. Reckitt Benckiser Pharmaceuticals, Inc. Richmond, VA; December 2014. **6.** Suboxone (buprenorphine and naloxone) [package insert]. Reckitt Benckiser Pharmaceuticals, Inc. Richmond, VA; February 2017. **7.** Probuphine (buprenorphine) [package insert]. Titan Pharmaceuticals, Inc. San Francisco, CA; May 2016. **8.** Zubsolv (buprenorphine and naloxone) [package insert]. Orexo US, Inc. Morristown, NJ; December 2016. **9.** Bunavail (buprenorphine and naloxone) [package insert]. BioDelivery Sciences International, Inc. Raleigh, NC; April 2015. **10.** VIVITROL [prescribing information]. Waltham, MA: Alkermes, Inc; rev December 2015. **11.** *Diagnostic and Statistical Manual of Mental Disorders. 5th ed.* Washington, DC: American Psychiatric Association; 2013. **12.** National Institute on Drug Abuse (NIDA). *Principles of Drug Addiction Treatment: A Research-Based Guide.* 3rd ed. NIH publication No. 12-4180. https://www.drugabuse.gov/publications/principles-drug-addiction-treatment-research-based-guide-third-edition/preface. Updated December 2012. Accessed May 10, 2017. **13.** Center for Substance Abuse Treatment. *Detoxification and Substance Abuse Treatment*. Treatment Improvement Protocol (TIP) Series 45. DHHS Publication No. (SMA) 06-4131. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2006. https://store.samhsa.gov/shin/content/SMA13-4131/SMA13-4131.pdf. Accessed May 17, 2017. **14.** Polydorou S, Kleber HD. Detoxification of opioids. In: Galanter M, Kleber HD, eds. *Textbook of Substance Abuse Treatment*. 4th ed. Arlington, VA: American Psychiatric Publishers, Inc.; 2008: chap 19. **15.** Mayet S, Farrell M, Ferri M, Amato L, Davoli M. Psychosocial treatment for opiate abuse and dependence. *Cochrane Database Syst Rev*. 2005;(1):CD004330. **16.** Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) national practice guideline for the use of medications in the treatment of addiction involving opioid use. *J Addict Med*. 2015;9(5):358-367. **17.** Dugosh K, Abraham A, Seymour B, McLoyd K, Chalk M, Festinger D. A systematic review on the use of psychosocial interventions in conjunction with medications for the treatment of opioid addiction. *J Addict Med*. 2016;10(2):93-103. **18.** National Institute on Drug Abuse (NIDA). *Drugs, Brains, and Behavior: the Science of Addiction*. NIH publication 14-5605. https://www.drugabuse.gov/publications/drugs-brains-behavior-science-addiction/drugs-brain. Updated July 2014. Accessed May 15, 2017. **19.** Saloner B, Karthikeyan S. Changes in substance abuse treatment use among individuals with opioid use disorders in the United States, 2004-2013. *JAMA*. 2015;314(14):1515-1517. **20.** American Psychiatric Association. Practice guideline for the treatment of patients with substance use disorders. Second edition. 2010. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/substanceuse.pdf. Accessed October 17, 2017. **21.** Center for Substance Abuse Treatment. *Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs*. Treatment Improvement Protocol (TIP) Series 43. HHS Publication No. (SMA) 12-4214. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2005. Revised 2017. **22.** American Society of Addiction Medicine. *Advancing Access to Addiction Medications: Implications for Opioid Addiction Treatment*. https://www.asam.org/docs/default-source/advocacy/aaam_implications-for-opioid-addiction-treatment_final. Published 2013. Accessed May 18, 2017. **23.** Methadose [package insert]. Mallinckrodt, Inc.: Hazelwood, MO; December 2016. **24.** U.S. Department of Justice Drug Enforcement Administration. Drug schedules. http://www.justice.gov/dea/druginfo/ds.shtml. Accessed May 18, 2017. **25.** Substance Abuse and Mental Health Services Administration. Methadone. https://www.samhsa.gov/medication-assisted-treatment/treatment/methadone. Updated September 28, 2015. Accessed May 16, 2017. **26.** Medline Plus. Buprenorphine Sublingual and Buccal (opioid dependence). https://medlineplus.gov/druginfo/meds/a605002.html. Revised January 15, 2017. Accessed August 2, 2017. **27.** Kosten TR, George TP. The neurobiology of opioid dependence: implications for treatment. *Sci Pract Perspect*. 2002;1(1):13-20. **28.** Center for Substance Abuse Treatment. *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction*. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2004. https://www.ncbi.nlm.nih.gov/books/NBK64245/pdf/Bookshelf_NBK64245.pdf. Accessed May 17, 2017. **29.** Collins CB, McAllister MS, Adury K. Drug abuse and addiction. In: *Cleveland Clinic: Current Clinical Medicine*. 2nd ed. Philadelphia, PA: Saunders, an Imprint of Elsevier; 2010:995-1000. **30.** ReVia (naltrexone hydrochloride tablets USP) [package insert]. Duramed Pharmaceuticals, Inc. Pomona, NY; October 2013. **31.** Substance Abuse and Mental Health Services Administration. *The Facts About Naltrexone for Treatment of Opioid Addiction*. HHS Publication No. (SMA) 12-4444. https://store.samhsa.gov/shin/content/SMA09-4444/SMA09-4444.pdf. Published 2009. Revised 2012. Accessed May 17, 2017. **32.** Hutchinson E, Catlin M, Andrilla CH, Baldwin LM, Rosenblatt RA. Barriers to primary care physicians prescribing buprenorphine. *Ann Fam Med*. 2014;12(2):128-133. **33.** Quest TL, Merrill JO, Roll J, Saxon AJ, Rosenblatt RA. Buprenorphine therapy for opioid addiction in rural Washington: the experience of the early adopters. *J Opioid Manag*. 2012;8(1):29-38. **34.** Substance Abuse and Mental Health Services Administration. Buprenorphine waiver management. http://www.samhsa.gov/medication-assisted-treatment/buprenorphine-waiver-management. Updated February 9, 2017. Accessed May 18, 2017. **35.** Institute for Clinical and Economic Review. *Management of Patients with Opioid Dependence: A Review of Clinical, Delivery System, and Policy Options*. http://icer-review.org/wp-content/uploads/2014/04/CEPAC-Opioid-Dependence-Final-Report-For-Posting-July-211.pdf. Published July 2014. Accessed May 18, 2017. **36.** McMurphy S, Shea J, Switzer J, Turner BJ. Clinic-based treatment for opioid dependence: a qualitative inquiry. *Am J Health Behav*. 2006;30(5):544-554. **37.** Uebelacker LA, Bailey G, Herman D, Anderson B, Stein M. Patients' beliefs about medications are associated with stated preference for methadone, buprenorphine, naltrexone, or no medication-assisted therapy following inpatient opioid detoxification. *J Subst Abuse Treat*. 2016;66:48-53. **38.** Substance Abuse and Mental Health Services Administration. *Pocket Guide. Medication-Assisted Treatment of Opioid Use Disorder*. https://store.samhsa.gov/shin/content//SMA16-4892PG/SMA16-4892PG.pdf. Accessed June 26, 2017. **39.** Teruya C, Schwartz RP, Mitchell SG, et al. Patient perspectives on buprenorphine/naloxone: a qualitative study of retention during the starting treatment with agonist replacement therapies (START) study. *J Psychoactive Drugs*. 2014;46(5):412-426. **40.** Suzuki J, Ellison TV, Connery HS, Surber C, Renner JA. Training in buprenorphine and office-based opioid treatment: a survey of psychiatry residency training programs. *Acad Psychiatry*. 2016;40(3):498-502.

IMPORTANT SAFETY INFORMATION

INDICATIONS

VIVITROL® (naltrexone for extended-release injectable suspension) is indicated for:

- Treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with VIVITROL. Patients should not be actively drinking at the time of initial VIVITROL administration.
- Prevention of relapse to opioid dependence, following opioid detoxification.
- VIVITROL should be part of a comprehensive management program that includes psychosocial support.

CONTRAINDICATIONS

VIVITROL is contraindicated in patients:

- Receiving opioid analgesics
- With current physiologic opioid dependence
- In acute opioid withdrawal
- Who have failed the naloxone challenge test or have a positive urine screen for opioids
- Who have exhibited hypersensitivity to naltrexone, polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other components of the diluent

WARNINGS AND PRECAUTIONS

Vulnerability to Opioid Overdose:

- After opioid detoxification, patients are likely to have a reduced tolerance to opioids. VIVITROL blocks the effects of exogenous opioids for approximately 28 days after administration. As the blockade wanes and eventually dissipates completely, use of previously tolerated doses of opioids could result in potentially life-threatening opioid intoxication (respiratory compromise or arrest, circulatory collapse, etc.).
- Cases of opioid overdose with fatal outcomes have been reported in patients who used opioids at the end of a dosing interval, after missing a scheduled dose, or after discontinuing treatment. Patients and caregivers should be told of this increased sensitivity to opioids and the risk of overdose.
- Although VIVITROL is a potent antagonist with a prolonged pharmacological effect, the blockade produced by VIVITROL is surmountable. The plasma concentration of exogenous opioids attained immediately following their acute administration may be sufficient to overcome the competitive receptor blockade. This poses a potential risk to individuals who attempt, on their own, to overcome the blockade by administering large amounts of exogenous opioids.
- Any attempt by a patient to overcome the VIVITROL blockade by taking opioids may lead to fatal overdose. Patients should be told of the serious consequences of trying to overcome the opioid blockade.

Injection Site Reactions:

- VIVITROL injections may be followed by pain, tenderness, induration, swelling, erythema, bruising, or pruritus; however, in some cases injection site reactions may be very severe.
- Injection site reactions not improving may require prompt medical attention, including, in some cases, surgical intervention.
- Inadvertent subcutaneous/adipose layer injection of VIVITROL may increase the likelihood of severe injection site reactions.
- Select proper needle size for patient body habitus, and use only the needles provided in the carton.
- Patients should be informed that any concerning injection site reactions should be brought to the attention of their healthcare provider.

Precipitation of Opioid Withdrawal:

- When withdrawal is precipitated abruptly by administration of an opioid antagonist to an opioid-dependent patient, the resulting withdrawal syndrome can be severe. Some cases of withdrawal symptoms have been severe enough to require hospitalization, and in some cases, management in the ICU.
- To prevent occurrence of precipitated withdrawal, opioid-dependent patients, including those being treated for alcohol dependence, should be opioid-free (including tramadol) before starting VIVITROL treatment:
  - An opioid-free interval of a minimum of 7–10 days is recommended for patients previously dependent on short-acting opioids.
  - Patients transitioning from buprenorphine or methadone may be vulnerable to precipitated withdrawal for as long as two weeks.
- If a more rapid transition from agonist to antagonist therapy is deemed necessary and appropriate by the healthcare provider, monitor the patient closely in an appropriate medical setting where precipitated withdrawal can be managed.
- Patients should be made aware of the risk associated with precipitated withdrawal and be encouraged to give an accurate account of last opioid use.

Hepatotoxicity:

- Cases of hepatitis and clinically significant liver dysfunction have been observed in association with VIVITROL. Warn patients of the risk of hepatic injury; advise them to seek help if experiencing symptoms of acute hepatitis. Discontinue use of VIVITROL in patients who exhibit acute hepatitis symptoms.

Depression and Suicidality:

- Alcohol- and opioid-dependent patients taking VIVITROL should be monitored for depression or suicidal thoughts. Alert families and caregivers to monitor and report the emergence of symptoms of depression or suicidality.

When Reversal of VIVITROL Blockade Is Required for Pain Management:

- For VIVITROL patients in emergency situations, suggestions for pain management include regional analgesia or use of non-opioid analgesics. If opioid therapy is required to reverse the VIVITROL blockade, patients should be closely monitored by trained personnel in a setting staffed and equipped for CPR.

Eosinophilic Pneumonia:

- Cases of eosinophilic pneumonia requiring hospitalization have been reported. Warn patients of the risk of eosinophilic pneumonia and to seek medical attention if they develop symptoms of pneumonia.

Hypersensitivity Reactions:

- Patients should be warned of the risk of hypersensitivity reactions, including anaphylaxis.

Intramuscular Injections:

- As with any IM injection, VIVITROL should be administered with caution to patients with thrombocytopenia or any coagulation disorder.

Alcohol Withdrawal:

- Use of VIVITROL does not eliminate nor diminish alcohol withdrawal symptoms.

ADVERSE REACTIONS

- Serious adverse reactions that may be associated with VIVITROL therapy in clinical use include severe injection site reactions, eosinophilic pneumonia, serious allergic reactions, unintended precipitation of opioid withdrawal, accidental opioid overdose, and depression and suicidality.
- The adverse events seen most frequently in association with VIVITROL therapy for alcohol dependence (ie, those occurring in ≥5% and at least twice as frequently with VIVITROL than placebo) include nausea, vomiting, injection site reactions (including induration, pruritus, nodules, and swelling), muscle cramps, dizziness or syncope, somnolence or sedation, anorexia, decreased appetite or other appetite disorders.
- The adverse events seen most frequently in association with VIVITROL in opioid-dependent patients (ie, those occurring in ≥2% and at least twice as frequently with VIVITROL than placebo) were hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache.

You are encouraged to report side effects to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see accompanying Prescribing Information and Medication Guide. Review the Medication Guide with your patients.