



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 3: UNDERSTANDING THE USE OF VIVITROL® (NALTREXONE FOR EXTENDED-RELEASE INJECTABLE SUSPENSION) IN APPROPRIATE PATIENTS

There is a persistent need for the healthcare community to actively address the opioid crisis in the United States. According to 2016 government statistics, an estimated 1.99 million American adults have an opioid use disorder.¹ Yet, available treatments remain underutilized.² Clinicians play an important role in ensuring that patients seeking help for opioid dependence have access to appropriate therapies (see **Issue 2**).

This newsletter will provide an overview of VIVITROL® (naltrexone for extended-release injectable suspension), a treatment option for the prevention of relapse to opioid dependence after detoxification, when used with counseling. This overview of VIVITROL will include its indications and contraindications, mechanism of action, relevant efficacy and safety trial data, Important Safety Information, and dosing and administration.

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 medication-assisted treatments (MATs).³⁻⁹ The fifth edition of the text 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).¹⁰ The former term is used in this newsletter to be consistent with the approved indication for numerous MAT options, including VIVITROL.

What Is VIVITROL?

Available MAT options for opioid dependence include full opioid agonists, partial agonists, and antagonists (see **Issue 2**).¹¹ VIVITROL is a monthly extended-release injectable formulation of an opioid antagonist called naltrexone, which blocks opioid receptors without activating them.^{9,12}

Please see Important Safety Information for VIVITROL throughout this newsletter. Please see accompanying Prescribing Information and Medication Guide. Review the Medication Guide with your patients.

Participating Steering Committee Members*

Laura P. Bamford, M.D., M.S.C.E.

Medical Director
Clinica Bienestar
Staff Physician
Jonathan Lax Treatment Center
Clinical Assistant Professor of Medicine
Perelman School of Medicine
University of Pennsylvania
Philadelphia, PA

Linda J. Frazier, M.A., R.N., M.C.H.E.S.

Director of Addictions Initiatives
Advocates for Human Potential Inc. (AHP)
Sudbury, MA

Thomas R. Kosten, M.D.

Waggoner Chair and Professor of Psychiatry
Department of Psychiatry
Baylor College of Medicine
Director
Division of Addictions
VA Medical Center
Houston, TX

Laura G. Leahy, Dr.N.P., A.P.R.N., F.A.A.N.P.

Board Certified Psychiatric & Addictions
Advanced Practice Nurse
Master Clinician in Psychopharmacology
Fellow in the American Association of
Nurse Practitioners
APNSolutions, LLC
Sewell, NJ

Paolo Mannelli, M.D.

Associate Professor
Department of Psychiatry and
Behavioral Sciences
Duke University
Associate Medical Director
Division of Addiction
Duke Addictions Program
Durham, NC

*The above Steering Committee members reviewed the content of this newsletter but did not author it. All members are paid consultants of Alkermes, Inc. Visit MeetingTheNeed.CurrentPsychiatry.com for a list of faculty disclosures.



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Vivitrol
(naltrexone for extended-release
injectable suspension)

Indications and contraindications

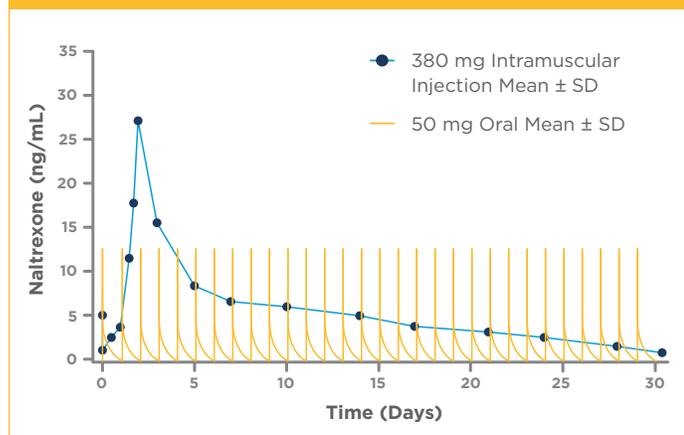
VIVITROL is indicated for the prevention of relapse to opioid dependence, following opioid detoxification.⁹ VIVITROL should be part of a comprehensive management program that includes psychosocial support.⁹ VIVITROL also is indicated for the treatment of alcohol dependence in patients who are able to 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.⁹

VIVITROL is contraindicated in patients receiving opioid analgesics, patients with current physiologic opioid dependence, or patients in acute opioid withdrawal.⁹ VIVITROL is also contraindicated in patients who have failed the naloxone challenge test, have a positive urine screen for opioids, or have previously exhibited hypersensitivity to naltrexone, polylactide-co-glycolide, carboxymethylcellulose, or any other components of the diluent.⁹

Please see additional Important Safety Information about VIVITROL throughout this newsletter.

The naltrexone in VIVITROL is formulated in microspheres, which break down slowly over the course of 4 weeks (Figure 1), allowing the antagonist to block opioid receptors continuously until the next monthly injection appointment.^{9,12}

Figure 1. VIVITROL Delivery Over the Approved Dosing Interval: Mean Naltrexone Concentration.^{13,14*}



*Plasma concentrations do not necessarily correlate with clinical efficacy. SD, standard deviation.

VIVITROL is a non-addictive, non-narcotic treatment option that is not associated with diversion.^{9,12} It has no known abuse potential.¹⁵ VIVITROL is not a scheduled product and does not require any special training to prescribe. VIVITROL is given through intramuscular (IM) injection by a healthcare provider.⁹

It is recommended that patients stop taking opioids or opioid-containing medications for a minimum of 7 to 10 days before starting VIVITROL to avoid precipitation of opioid withdrawal, which may be severe.⁹

How VIVITROL works

Opioid dependence exploits the brain's natural mechanisms of pleasure and reward.^{12,16} When someone takes an opioid, the drug binds to and activates the mu opioid receptors in

the limbic system.¹² (See **Issue 1** for information about the pathophysiology of opioid dependence.) Treatment for opioid dependence often involves medications that bind to the mu opioid receptor.¹² An opioid antagonist, such as VIVITROL, binds very strongly to the mu opioid receptor without activating it.^{9,12,17} VIVITROL is able to competitively block the effects of opioid drugs for up to 1 month.^{9,12} VIVITROL is not aversive therapy and does not cause a disulfiram-like reaction as a result of either opioid use or ethanol ingestion.⁹

Vulnerability to opioid overdose

Note that 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.).⁹

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.

An opioid antagonist, such as VIVITROL, binds very strongly to the mu opioid receptor without activating it.^{9,12,17}

VIVITROL Pivotal Trial in Opioid-Dependent Patients

The safety and efficacy of VIVITROL has been studied in a 24-week, multicenter, double-blind, randomized, placebo-controlled trial of opioid-dependent outpatients aged 18 years or older.¹⁸ Diagnoses of opioid dependence were established according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision).¹⁸ Prior to treatment initiation, patients were voluntarily seeking treatment, completing up to 30 days of inpatient opioid detoxification, and off opioids for at least 7 days.¹⁸ Participants were randomized to receive VIVITROL (n=126) or placebo (n=124).¹⁸ Patients received a urine drug test every week, psychosocial support every 2 weeks, and a treatment injection every 4 weeks.¹⁸

Please see Important Safety Information for VIVITROL throughout this newsletter. Please see accompanying Prescribing Information and Medication Guide. Review the Medication Guide with your patients.

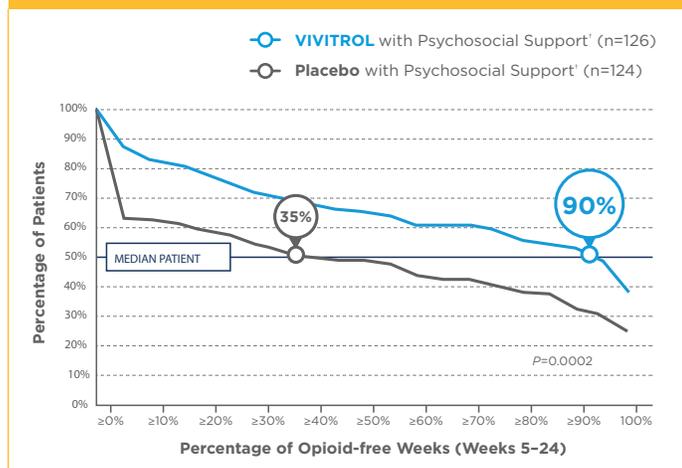
Note that additional studies and analyses of the efficacy and safety of VIVITROL have been conducted since the completion of this pivotal trial, but they are not the focus of this review.¹⁹⁻²¹

Efficacy data PRIMARY ENDPOINT

The primary endpoint was the response profile for confirmed abstinence during Weeks 5 to 24.¹⁸ Weeks 1 to 4 were omitted from this endpoint to allow for stabilization of abstinence.¹⁸ Confirmed abstinence (“opioid free”) was defined as a negative urine drug test for opioids and no self-reported opioid use.¹⁸

With VIVITROL and psychosocial support, more patients achieved complete abstinence compared with placebo and psychosocial support. Complete abstinence was sustained by 36% (n=45) of VIVITROL patients compared with 23% (n=28) of patients treated with placebo during Weeks 5 to 24 ($P=0.0224$).¹⁸ The median VIVITROL patient had confirmed abstinence for 90% of the weeks in the evaluation period versus 35% for the median placebo patient ($P=0.0002$) (Figure 2).¹⁸

Figure 2. Subjects Sustaining Various Percentages of Opioid-Free* Weeks in the Period from Week 5 to Week 24.^{9,18}



*Confirmed abstinence, or “opioid free,” was defined as a negative urine drug test for opioids and no self-reported opioid use.

*Psychosocial support consisted of biweekly counseling sessions of individual drug counseling, adapted for opioid dependence. Data were not collected during Weeks 1 to 4 of the trial to allow for stabilization of abstinence.

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 to 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 2 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

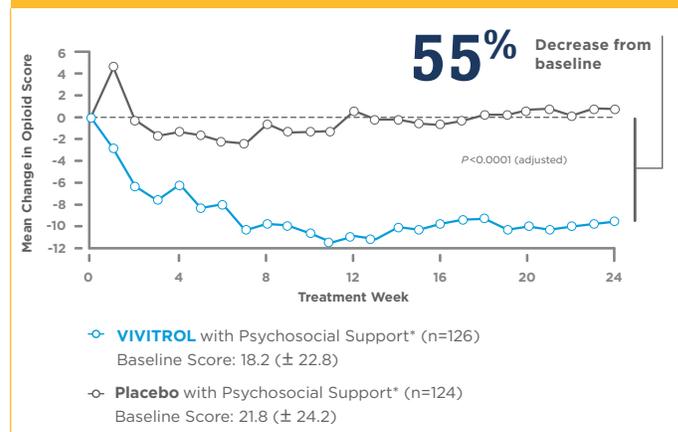
appropriate medical setting where precipitated withdrawal can be managed. Patients should be made aware of the risk associated with precipitated withdrawal and be encouraged to give an accurate account of last opioid use.

SECONDARY ENDPOINTS

Secondary endpoints were self-reported opioid craving scores, self-reported opioid-free days, number of days of retention, and relapse to physiological opioid dependence.¹⁸

Craving (described as a “need for opioids”) was reported weekly according to a visual analog scale (VAS) of 0 to 100, with 0 being “not at all” and 100 “very much so.”¹⁸ A statistically and clinically significant reduction in opioid craving was observed with VIVITROL versus placebo by Week 8 ($P=0.0048$), persisting every week through Week 24 ($P<0.0001$).¹⁸ VIVITROL patients had a mean change from baseline of -10.1 points versus a mean change of +0.7 points for patients in the placebo group over 6 months (baseline mean VAS score, 20). Patients given VIVITROL had a 55% decrease in self-reported opioid craving from baseline to Week 24 (Figure 3).¹⁸ Patients given placebo had a 3% increase in craving from baseline to Week 24.¹⁸

Figure 3. Mean Change in Self-Reported Craving.^{18,22}



*Psychosocial support consisted of biweekly individual drug counseling sessions, adapted for opioid dependence.

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

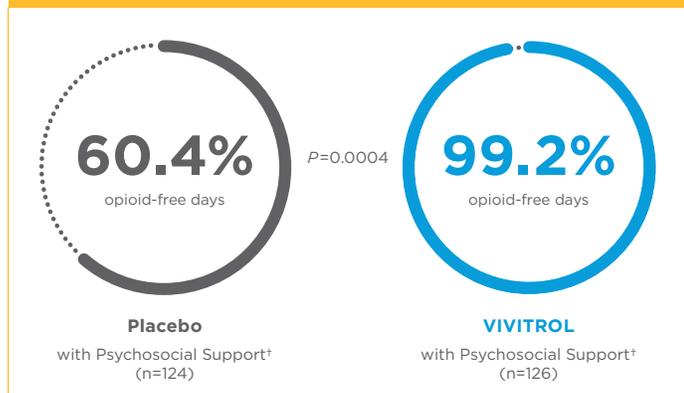
For VIVITROL patients in emergency situations, suggestions for pain management include regional analgesia or use of non-opioid analgesics. If opioid therapy is required to reverse the VIVITROL blockade, patients should be closely monitored by trained personnel in a setting staffed and equipped for CPR.

Please see Important Safety Information for VIVITROL throughout this newsletter. Please see accompanying Prescribing Information and Medication Guide. Review the Medication Guide with your patients.

Patients in the VIVITROL group reported a median of 99.2% opioid-free days compared with 60.4% in the placebo group ($P=0.0004$) (Figure 4).¹⁸ The median number of opioid-free days at baseline was zero for both the VIVITROL and placebo groups.²²

VIVITROL also helped significantly more patients complete 24 weeks (168 days) of treatment ($n=67$ [53%]) compared with placebo ($n=47$ [38%]; $P=0.0171$).¹⁸ The median time in treatment was more than 168 days for patients taking VIVITROL versus 96 days for those taking placebo ($P=0.0042$).¹⁸

Figure 4. Opioid-Free Days During Weeks 1 to 24.^{18*}



*"Opioid-free" was defined as no self-reported opioid use.

†Psychosocial support consisted of biweekly individual drug counseling sessions, adapted for opioid dependence.

Only 1 patient on VIVITROL (<1%) discontinued due to positive naloxone challenge, indicating relapse to physiological opioid dependence and risk of precipitated withdrawal, compared to 17 patients on placebo (14%; $P<0.0001$). With VIVITROL, there were 94% fewer naloxone-confirmed relapses to opioid dependence.¹⁸

Dosing and administration

VIVITROL must be prepared and administered by a healthcare provider. Full instructions are provided within the VIVITROL prescribing information. Prior to initiating VIVITROL, an opioid-free duration of a minimum of 7 to 10 days is recommended for patients, to avoid precipitation of opioid withdrawal that may be severe enough to require hospitalization.⁹

The recommended dose of VIVITROL is 380 mg delivered intramuscularly every 4 weeks, or once a month. The injection should be administered by a healthcare provider as an intramuscular (IM) gluteal injection, alternating buttocks for each subsequent injection, using the carton components provided.⁹

The needles provided in the carton are customized needles. VIVITROL must not be injected using any other needle. The needle lengths (either 1 ½ or 2 inches) may not be adequate in every patient because of body habitus. Body habitus should be assessed prior to each injection for each patient to assure that needle length is adequate for intramuscular administration. For patients with a larger

amount of subcutaneous tissue overlying the gluteal muscle, the administering healthcare provider may utilize the supplied 2-inch needle with needle protection device to help ensure that the injectate reaches the intramuscular mass. For very lean patients, the 1 ½-inch needle may be appropriate to prevent the needle contacting the periosteum. Either needle may be used for patients with average body habitus.⁹

Healthcare providers should ensure that the VIVITROL injection is given correctly, and should consider alternate treatment for those patients whose body habitus precludes an intramuscular gluteal injection with one of the provided needles.⁹

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.

VIVITROL must not be administered intravenously or subcutaneously.⁹

If a patient misses a dose, he/she should be instructed to receive the next dose as soon as possible. Pretreatment with oral naltrexone is not required before using VIVITROL.⁹

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 intramuscular 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

In this controlled trial, 2% of opioid-dependent patients treated with VIVITROL discontinued treatment due to an adverse event, as did 2% of the opioid-dependent patients treated with placebo.¹⁸

The adverse events seen most frequently in association with VIVITROL therapy in opioid-dependent patients (i.e., 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 (Table).^{9,18} **Refer to the VIVITROL Prescribing Information for a complete list of adverse events.**

Table. Adverse Reactions With VIVITROL vs. Placebo.^{9,18*}

	VIVITROL 380 mg with Psychosocial Support (n=126)	Placebo with Psychosocial Support (n=124)
ALT increased	13%	6%
AST increased	10%	2%
GGT increased	7%	3%
Nasopharyngitis	7%	2%
Insomnia	6%	1%
Influenza	5%	4%
Hypertension	5%	3%
Injection site pain	5%	1%
Toothache	4%	2%
Headache	3%	2%

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase.

*Adverse reactions that occurred in ≥2% of patients with opioid dependence treated with VIVITROL and occurred more frequently in the VIVITROL group versus the placebo group.

The adverse events seen most frequently in association with VIVITROL therapy for alcohol dependence (i.e., 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), arthralgia, arthritis, or joint stiffness, muscle cramps, dizziness or syncope, somnolence or sedation, anorexia, decreased appetite or other appetite disorders.

Getting VIVITROL for your patients

The fulfillment process for VIVITROL depends on the patient's health plan. If a patient's insurance classifies VIVITROL as a medical benefit and the prescription is taken to a retail pharmacy, the full cash price may be charged.

The prescription may be sent to a pharmacy (specialty or other) if the patient's health plan classifies VIVITROL as a medical benefit or a pharmacy benefit. If VIVITROL is classified as a medical benefit, another option is for the prescriber to buy units of VIVITROL from a specialty distributor and bill the patient's insurance directly when it is administered.

More information on how to get VIVITROL for your patients is available at vivitrol.com.

Conclusions

There is a persistent need to do everything possible to help address the opioid epidemic in the United States. As described in this newsletter, VIVITROL—along with psychosocial support—is an important MAT option to prevent relapse to opioid dependence after detoxification.⁹

Please refer to Issues 1 and 2 in this newsletter series for more information about opioid dependence as well as helping to overcome barriers to treatment. Visit MeetingTheNeed.CurrentPsychiatry.com.

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