THE WAY WE LOOK AT OPIOID AND ALCOHOL DEPENDENCE
EFFECTIVE CLINICAL UTILIZATION OF VIVITROL

PLEASE SEE IMPORTANT SAFETY INFORMATION THROUGHOUT THIS PRESENTATION. PRESCRIBING INFORMATION AND MEDICATION GUIDE WILL BE FURNISHED DURING THIS PROGRAM.
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*Paid speaker for Alkermes, Inc.
AGENDA

• THE SCOPE OF DEPENDENCE
• HOW DEPENDENCE WORKS
• RETHINKING OUR APPROACH
• INTRODUCING VIVITROL®
  (NALTREXONE FOR EXTENDED-RELEASE INJECTABLE SUSPENSION)

• EFFICACY AND SAFETY OF VIVITROL
  • IN ALCOHOL DEPENDENCE
  • IN OPIOID DEPENDENCE
• OPEN FOR DISCUSSION

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THE SCOPE OF THE PROBLEM
Among Americans (18+)
oopioid dependence

INCREASED

>50%

from 2002 to 2011\textsuperscript{1,2}

Includes heroin and prescription opioids
In 2010, nearly **8 MILLION** AMERICANS (18+) WERE DEPENDENT ON ALCOHOL \(^1\)
7 out of 10 opioid users relapse within one month of inpatient detox.
HOW DEPENDENCE WORKS
DEPENDENCE AFFECTS 2 REGIONS OF THE BRAIN

THE CORTEX

THE LIMBIC REGION
role of the LIMBIC REGION

- basic drives and urges
- rewards
- pleasure
OPIOIDS IN THE LIMBIC REGION
RELEASE OF DOPAMINE
ALCOHOL IN THE LIMBIC REGION
ALCOHOL CONSUMPTION CAUSES AN INCREASED RELEASE OF β-ENDORPHINS
β-ENDORPHINS BIND TO µ-OPIOID RECEPTORS
INCREASING THE RELEASE OF DOPAMINE
RESULTING IN FEELINGS OF PLEASURE
DEPENDENCE AFFECTS 2 REGIONS OF THE BRAIN

THE CORTEX

THE LIMBIC REGION
role of the CORTEX
– decision making
– thinking
– reasoning
– planning
CONDITIONING AND CRAVING

Drug experience is associated with environmental cues that act as learned “triggers” that can persist and re-emerge even after years of abstinence\textsuperscript{1,2}. 

\textsuperscript{1}

\textsuperscript{2}
RETHINKING OUR APPROACH
Often, treatment models include detox from opioids or alcohol without subsequent pharmacological support.¹,²

- First weeks following opioid detox are the most dangerous for relapse or overdose³
- Barriers to adoption and implementation exist on multiple levels¹
- Medication should complement psychosocial support⁴
Since dependence affects both the cortex and the limbic region, a comprehensive treatment plan should include both psychosocial support and pharmacotherapy.¹

ONGOING TREATMENT

COUNSELING
- teaching skills necessary to cope with triggers and life stressors without drugs

USING MEDICATION
- after detoxification to treat opioid and alcohol dependence
“No single treatment is appropriate for everyone. Matching treatment settings, interventions, and services to an individual’s particular problems and needs is critical to his or her ultimate success.”

–National Institute on Drug Abuse
There's no single reason for relapse. Relapses indicate that treatment needs to be reinstated or adjusted, or alternate treatment is needed.²
TO HELP PREVENT RELAPSE

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Vivitrol®
(naltrexone for extended-release injectable suspension)
WHAT IT IS:

WHAT IT ISN’T:
VIVITROL® IS¹:

MONTHLY EXTENDED-RELEASE INJECTABLE NALTREXONE
HCP ADMINISTERED
OPIOID ANTAGONIST
PART OF A COMPREHENSIVE MANAGEMENT PROGRAM THAT INCLUDES PSYCHOSOCIAL SUPPORT

If your patients take opioids or opioid-containing medications, such as prescription pain medications or street drugs, it is recommended they stop these for a minimum of 7 to 10 days before starting VIVITROL® to avoid precipitation of opioid withdrawal that may be severe enough to require hospitalization.

Patients should be able to abstain from drinking in an outpatient setting before starting VIVITROL®.

VIVITROL® may not work for everyone.

More Important Safety Information about VIVITROL® will be discussed later.
If your patients take opioids or opioid-containing medications, such as prescription pain medications or street drugs, it is recommended they stop these for a minimum of 7 to 10 days before starting VIVITROL® to avoid precipitation of opioid withdrawal that may be severe enough to require hospitalization.

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VIVITROL® may not work for everyone.

More Important Safety Information about VIVITROL® will be discussed later.
WHO VIVITROL® IS FOR

INDICATIONS

VIVITROL® is indicated for:

• Treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting. 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
HOW VIVITROL® WORKS

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VIVITROL BLOCKS µ-OPIOID RECEPTORS

PREVENTING OPIOIDS FROM INTERACTING WITH THE RECEPTOR

PREVENTING THE EXCESSIVE RELEASE OF DOPAMINE
Although the mechanism of action in alcohol dependence is not fully understood, this blockade is thought to prevent the increased dopamine release responsible for the pleasurable reinforcing effects of alcohol\textsuperscript{1-4}. 

References: 
INJECTION SITE REACTION WARNING

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® ADMINISTRATION¹

- VIVITROL® should be administered by a healthcare professional
- VIVITROL® 380 mg is given as an IM gluteal injection every 4 weeks, or once a month
- VIVITROL® should be injected into the upper, outer quadrant of the buttock, deep into the muscle
- The buttock should be alternated per monthly injection
- VIVITROL® should be administered with caution to patients with thrombocytopenia or any coagulation disorder
- VIVITROL® must not be administered intravenously or subcutaneously

VIVITROL delivers medication continuously over the approved dosing interval²

Mean naltrexone concentration*

- VIVITROL 380 mg Intramuscular Injection

*Plasma concentrations do not necessarily correlate with clinical efficacy.
REINITIATION OF TREATMENT IN PATIENTS PREVIOUSLY DISCONTINUED

• There are no data to specifically address reinitiation of treatment
• Patients should be opioid-free at the time of dose administration

SWITCHING FROM ORAL NALTREXONE

• There are no systematically collected data that specifically address the switch from oral naltrexone to VIVITROL®

SWITCHING FROM BUPRENORPHINE, BUPRENORPHINE/NALOXONE, OR METHADONE

• There are no systematically collected data that specifically address the switch from buprenorphine or methadone to VIVITROL®; however, review of postmarketing case reports have indicated that some patients may experience severe manifestations of precipitated withdrawal when being switched from opioid agonist therapy to opioid antagonist therapy
• Patients transitioning from buprenorphine or methadone may be vulnerable to precipitation of withdrawal symptoms for as long as 2 weeks
• Healthcare providers should be prepared to manage withdrawal symptomatically with non-opioid medications
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VIVITROL IN ALCOHOL DEPENDENCE

6-month, double-blind trial with monthly injections\textsuperscript{1,2}

Initial screening of 899* participants

- 627 participants randomized into 3 groups
- 210 patients received VIVITROL 190 mg

209 PLACEBO

208 VIVITROL 380 mg

All groups received psychosocial support

*Patients with treated depression and stable pharmacotherapy for at least 8 weeks were not excluded.

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References:
VIVITROL IN ALCOHOL DEPENDENCE

6-month, double-blind trial with monthly injections

Primary study outcome

Patients treated with VIVITROL® 380 mg had
25% fewer heavy-drinking days
than patients treated with placebo and psychosocial support.

$P = 0.03$

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In a prespecified subset, 8% of the study population (n=53) abstained from drinking for 7 days prior to the first injection.¹,²
In the prespecified subset, patients treated with VIVITROL® had 92% fewer heavy-drinking days.

Median heavy-drinking days per month:

<table>
<thead>
<tr>
<th>Placebo (with psychosocial support)</th>
<th>VIVITROL® 380 mg (with psychosocial support)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Baseline</td>
</tr>
<tr>
<td>15.2 days</td>
<td>15.2 days</td>
</tr>
<tr>
<td>PLACEBO</td>
<td>VIVITROL</td>
</tr>
<tr>
<td>2.5 days</td>
<td>0.2 days</td>
</tr>
<tr>
<td>Week 24</td>
<td>Week 24</td>
</tr>
</tbody>
</table>

The same treatment effects were not evident among the subset of patients (n=571) who were actively drinking at the time of treatment initiation.

References:
IMPORTANT SAFETY INFORMATION – WARNINGS AND PRECAUTIONS

PRECIPITATION OF OPIOID WITHDRAWAL

- Withdrawal precipitated by administration of VIVITROL® may be severe. Some cases of withdrawal symptoms have been severe enough to require hospitalization and management in the ICU.

- To prevent precipitated withdrawal in patients dependent on opioids, patients, including those being treated for alcohol dependence, should be opioid-free (including tramadol) for a minimum of 7 to 10 days before starting VIVITROL®.

- Patients transitioning from buprenorphine or methadone may be vulnerable to precipitated withdrawal for as long as two weeks.

- Patients should be made aware of the risk associated with precipitated withdrawal and be encouraged to give an accurate account of last opioid use.

- Healthcare providers should always be prepared to manage withdrawal symptomatically with non-opioid medications because there is no completely reliable method for determining whether a patient has had an adequate opioid-free period.
DEPRESSION AND SUICIDALITY

• Alcohol-dependent patients, including those taking VIVITROL, should be monitored for the development of depression or suicidal thinking.

• Families and caregivers of patients being treated with VIVITROL® should be alerted to the need to monitor patients for the emergence of symptoms of depression and suicidality, and to report such symptoms to the patient’s healthcare provider.

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
IMPORTANT SAFETY INFORMATION – WARNINGS AND PRECAUTIONS

ALCOHOL WITHDRAWAL

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

INTRAMUSCULAR INJECTIONS

• As with any intramuscular injection, VIVITROL should be administered with caution to patients with thrombocytopenia or any coagulation disorder (eg, hemophilia and severe hepatic failure).
• 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 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

To report SUSPECTED ADVERSE REACTIONS, contact Alkermes, Inc. at 1-800-VIVITROL (1-800-848-4876) and/or email: usmedinfo@alkermes.com, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch
VIVITROL® IN PREVENTING RELAPSE TO OPIOID DEPENDENCE

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6-month, double-blind trial with monthly injections

Participants screened after completion of detoxification
Required to abstain from opioids 7 days prior to treatment
Randomized into 2 groups

124 PLACEBO
126 VIVITROL 380 mg

Both groups received psychosocial support

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References:
Patients treated with VIVITROL® had higher rates of complete abstinence

All weekly visits (weeks 5-24)

- **23%** PLACEBO
  - Confirmed abstinence = negative urine drug test and no self-reported opioid use.
  - Complete abstinence = opioid-free at all weekly visits, weeks 5-24

- **36%** VIVITROL
  - Completely abstinent VIVITROL patients (with psychosocial support)

**P = 0.0224 (adjusted)**

Patients treated with VIVITROL® had significantly higher percentage of opioid-free weeks.1

During weeks 5-24

Primary study outcome

Confirmed abstinence = negative urine test and no self-reported opioid use

Median PLACEBO patient (with psychosocial support) had 35% cumulative opioid-free weeks

Median VIVITROL patient (with psychosocial support) had 90% cumulative opioid-free weeks

\[ P = 0.0002 \]

Patients treated with VIVITROL® had **55% decrease in self-reported opioid craving**¹

Secondary study endpoint  
Weeks 1-24

Craving was reported according to a visual analogue scale:  
Scale of 1-100  
0 = not at all  
100 = very much so

Patients treated with VIVITROL®
17x less likely to relapse to physical dependence

Secondary study endpoint
168-day double-blind period
* Relapse to physical dependence defined as positive naloxone challenge

14% (n=17) of patients on placebo (with psychosocial support) discontinued the study due to relapse to physical dependence.*

0.8% (n=1) of patients on VIVITROL (with psychosocial support) discontinued the study due to relapse to physical dependence.*

Includes lack of efficacy, withdrew consent, investigator judgment, lost to follow-up, major protocol violation, adverse events, incarceration, and patient relocation.


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The median VIVITROL® patient completed 100% of the study.\(^1\)

**Weeks 1-24**

- **Placebo**: 96 days
- **VIVITROL**: 168 days

\[ P = 0.004 \text{ (adjusted)} \]

The median VIVITROL patient (with psychosocial support) stayed in treatment for the full 168-day duration of the double-blind period.

The median placebo patient (with psychosocial support) stayed in treatment for 96 days.

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VULNERABILITY TO OPIOID OVERDOSE

- Because VIVITROL® blocks the effects of exogenous opioids for approximately 28 days after administration, patients are likely to have a reduced tolerance to opioids after opioid detoxification. As the blockade dissipates, 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 even with lower doses than used before.

- Any attempt by a patient to overcome the VIVITROL® blockade by taking opioids may lead to life-threatening intoxication or fatal overdose. Patients should be told of the serious consequences of trying to overcome the opioid blockade.
DEPRESSION AND SUICIDALITY

- Opioid-dependent patients, including those taking VIVITROL, should be monitored for the development of depression or suicidal thinking.
- Families and caregivers of patients being treated with VIVITROL® should be alerted to the need to monitor patients for the emergence of symptoms of depression and suicidality, and to report such symptoms to the patient’s healthcare provider.

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.

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.

HYPERSENSITIVITY REACTIONS

- Patients should be warned of the risk of hypersensitivity reactions, including anaphylaxis.
IMPORTANT SAFETY INFORMATION – 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® in opioid-dependent patients also include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache

To report SUSPECTED ADVERSE REACTIONS, contact Alkermes, Inc. at 1-800-VIVITROL (1-800-848-4876) and/or email: usmedinfo@alkermes.com, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch
APPLICATION IN THE REAL WORLD

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DISCUSSION

Given the information you’ve just seen, do you think there are appropriate patients in your practice who might benefit from VIVITROL for treatment of alcohol or opioid dependence?
THANK YOU