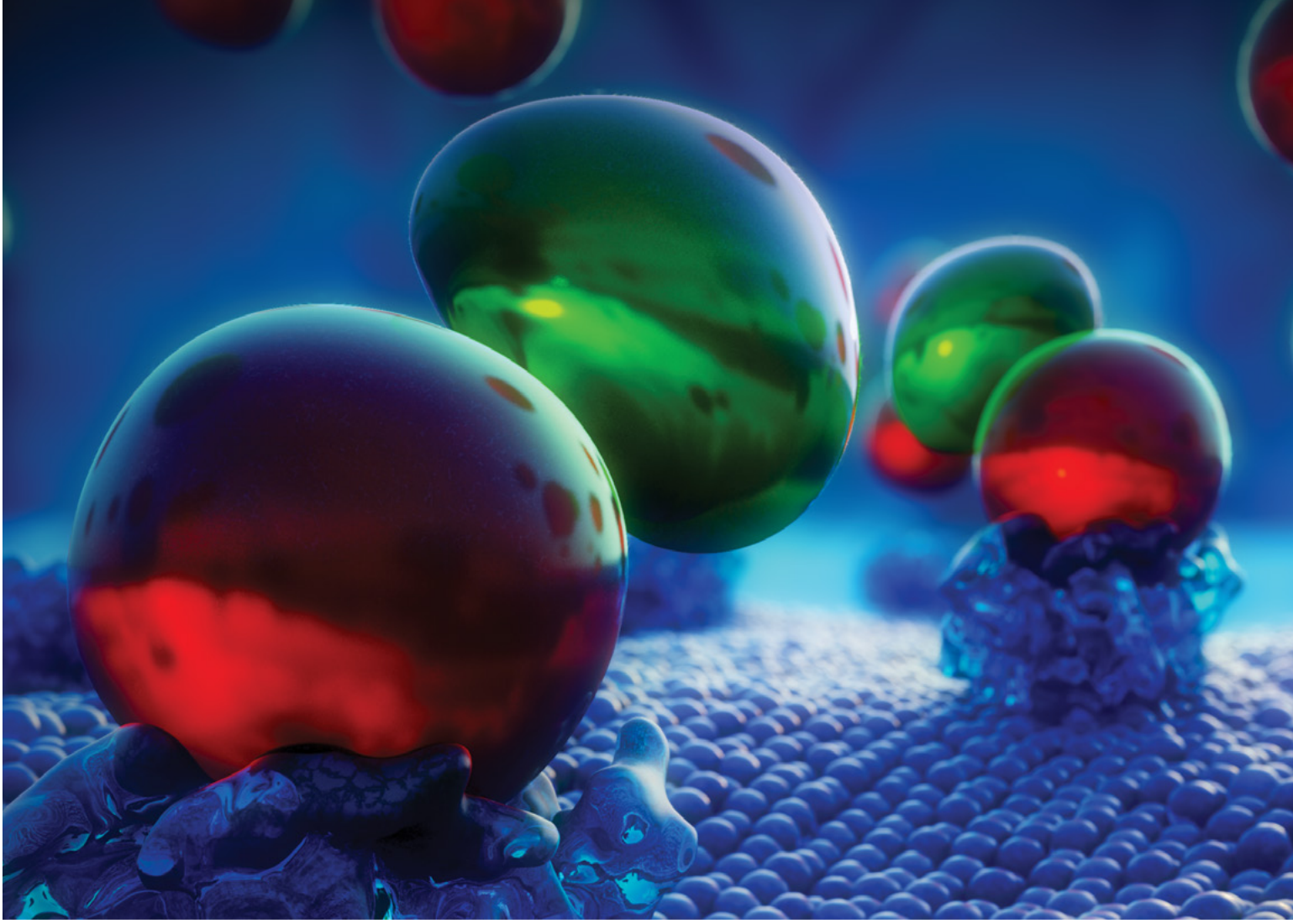

MECHANISM OF ACTION

VIVITROL® (naltrexone for extended-release injectable suspension) – A μ-Opioid Receptor Antagonist

VIVITROL is indicated for prevention of relapse to opioid dependence, following opioid detoxification. VIVITROL should be part of a comprehensive management program that includes psychosocial support.

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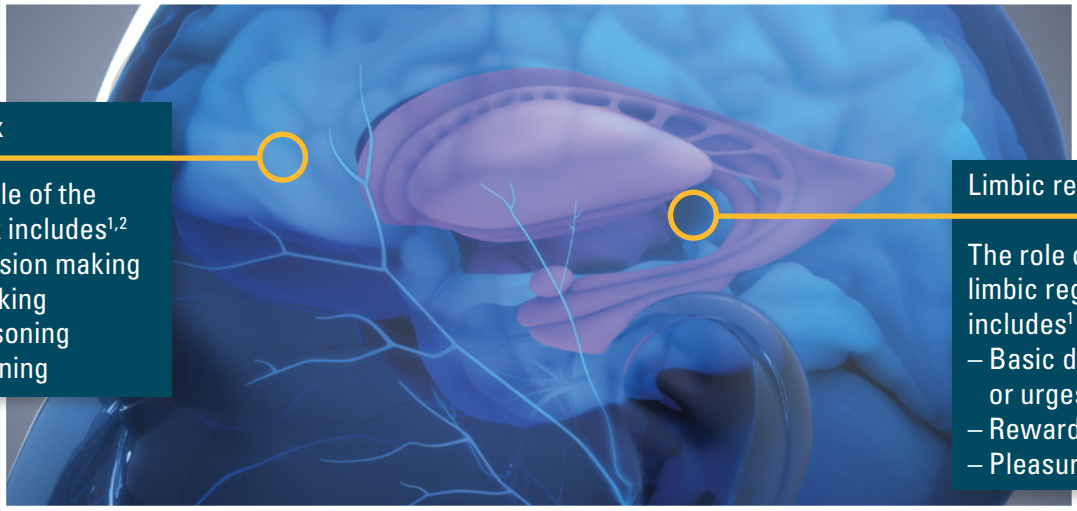
Opioid dependence is a chronic, relapsing brain disease

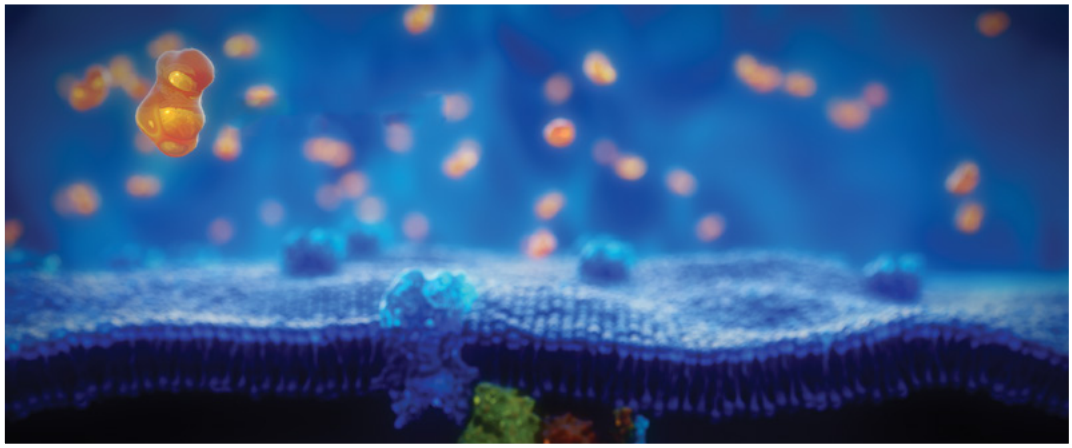
Opioid dependence affects 2 regions of the brain: the cortex and limbic region[1]



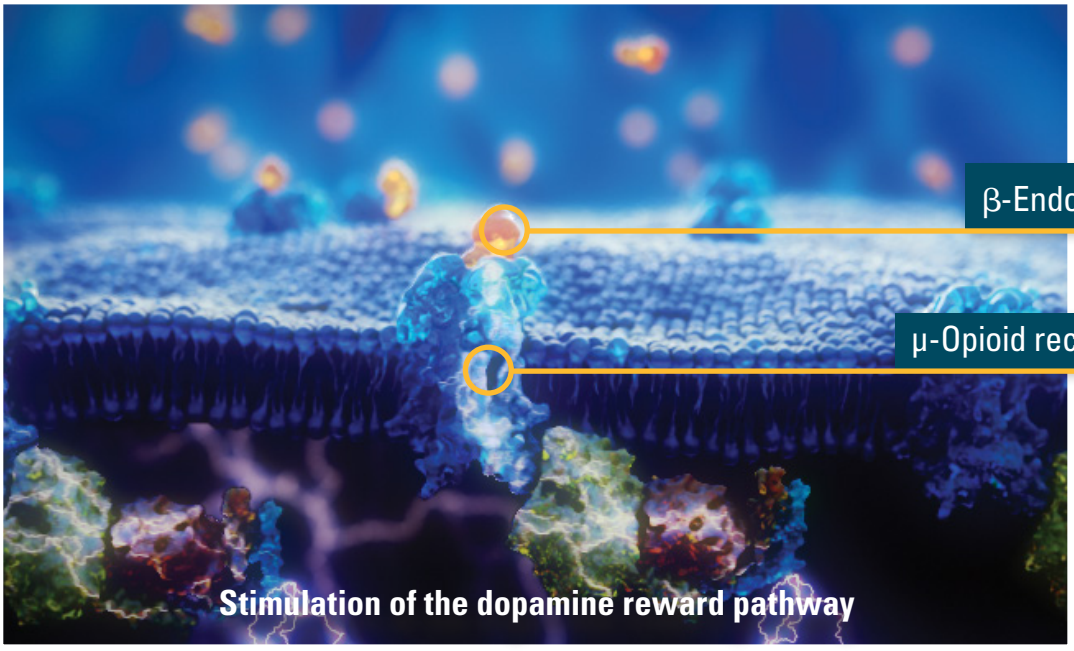
- Opioid dependence is a chronic, relapsing brain disease characterized by developing tolerance to opioids and exhibiting signs of physical withdrawal upon discontinuation[2,3]
- Dependence on drugs changes the brain's structure and how it works[2]
- Two regions of the brain, the cortex and limbic region, are affected by opioid dependence and can be targeted by comprehensive treatment, including medication and psychosocial therapy such as counseling[2]
- Counseling targets the cortex, which plays a role in[1,2]
  - Decision making
  - Thinking
  - Reasoning
  - Planning
- Medications target the limbic region, which regulates[1]
  - Basic drives or urges
  - Rewards
  - Pleasure

Endorphin activity in the normal brain

β-endorphins in the normal brain



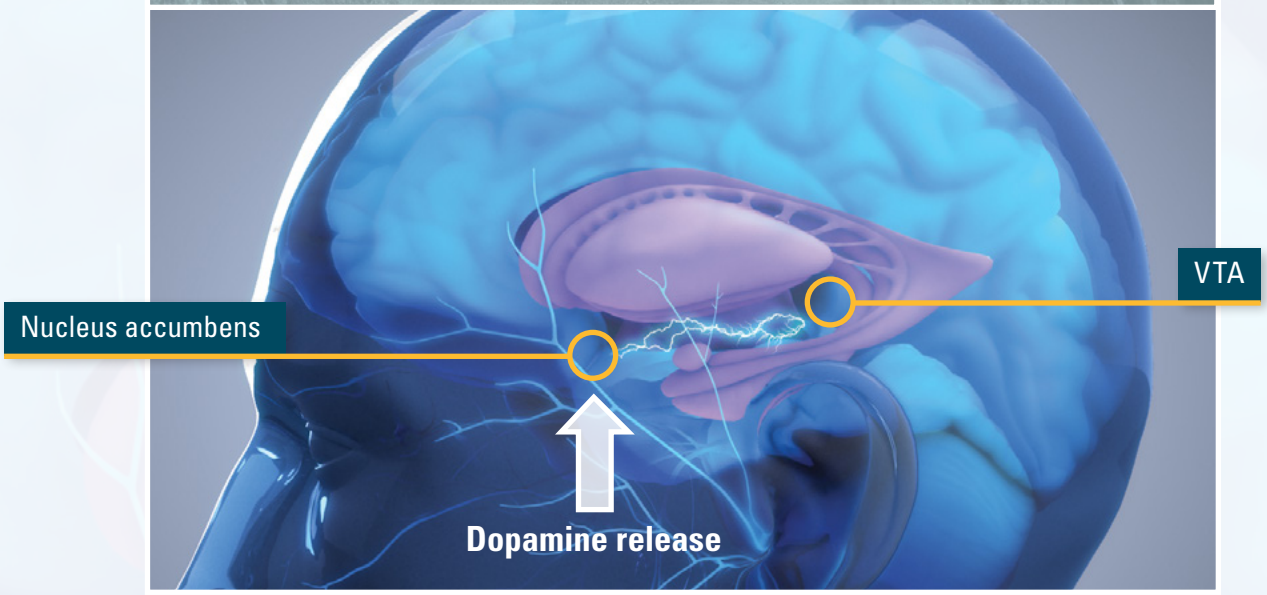
β-endorphin binding to a μ-opioid receptor in the brain



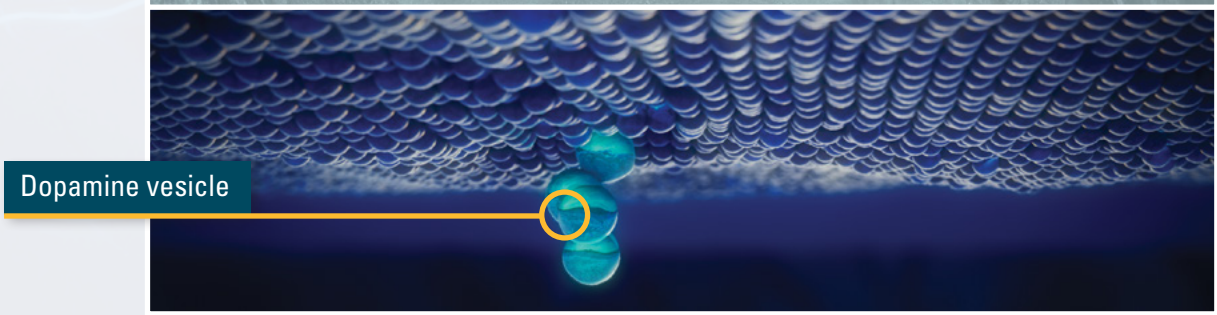
- Endorphins are endogenous opioids that are released in response to enjoyable activities such as physical exercise (eg, during a runner's "high")[4]
- The β-endorphins bind and activate μ-opioid receptors in the brain, stimulating the release of dopamine[5]
- Dopamine release promotes feelings of reward, pleasure, and euphoria[3]

Normal release of dopamine in the brain

The ventral tegmental area (VTA) regulates the dopamine reward pathway[3]



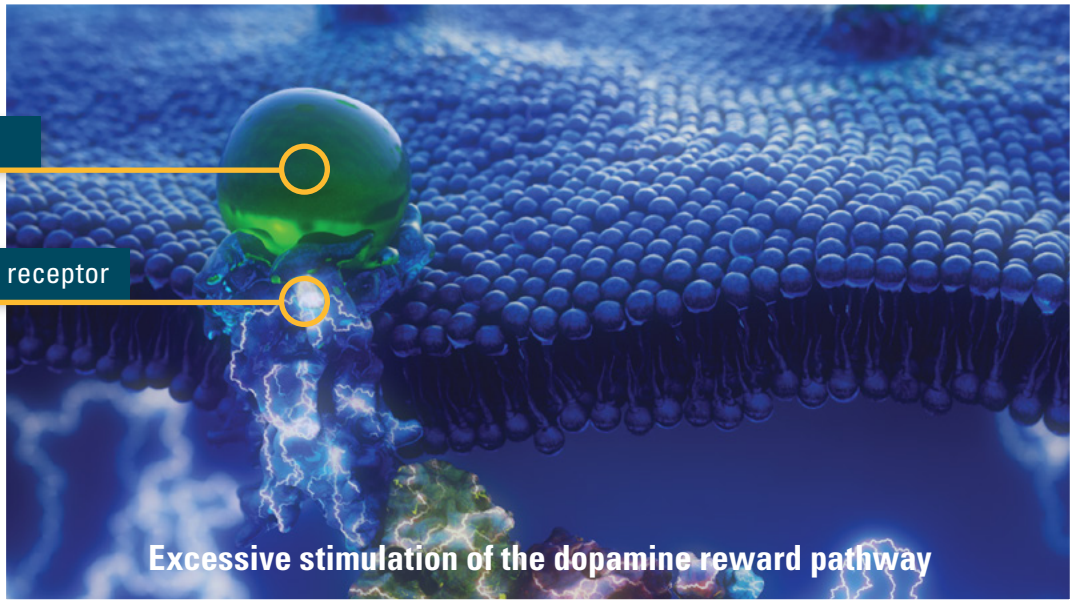
Normal dopamine release in the synapse



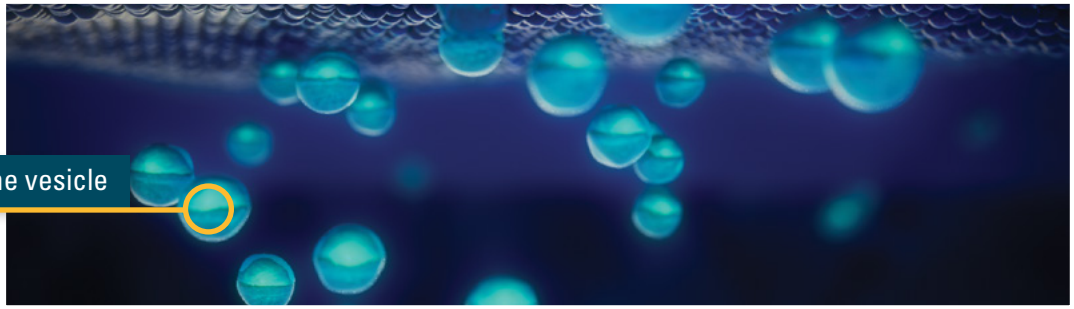
- The VTA, located within the mesolimbic system, is stimulated by different activities, including eating, exercise, and sex[3,6]
- Within the VTA, μ-opioid receptors found on the surface of neurons are stimulated by endogenous opioids such as β-endorphins[7]
- Activation of the VTA induces the release of dopamine into the nucleus accumbens[3]
- This dopamine release promotes feelings of pleasure, euphoria, and reward[1,3]
- Repeated episodes of pleasure, euphoria, and reward result in a learning process called reinforcement[1,3]
- Reinforcement motivates the individual to repeat behaviors that are pleasurable[1,3]

Opioid drugs and opioid pain relievers excessively stimulate the dopamine reward pathway

Opioid binding to a μ-opioid receptor



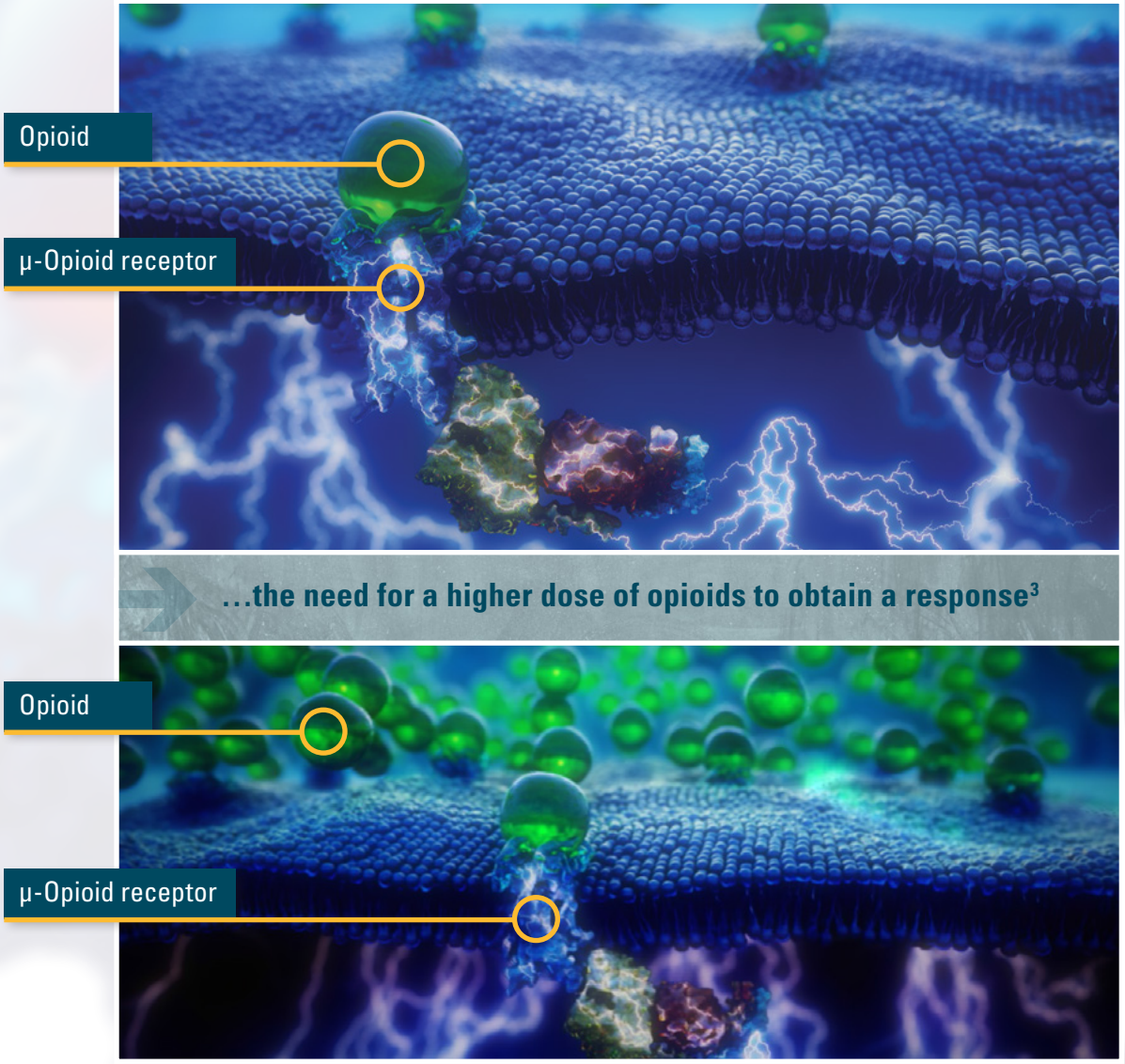
Excessive dopamine release in the synapse



- Normally, feelings of pleasure and reward are regulated by β-endorphins[7]
- Opioid drugs such as heroin or opioid analgesics, like oxycodone, produce a greater than normal signal by binding to μ-opioid receptors and stimulating the increased release of dopamine[3]
- The increased release of dopamine produces intense feelings of pleasure and euphoria[1,3]

Development of tolerance

Over time, repeated exposure to opioids leads to…

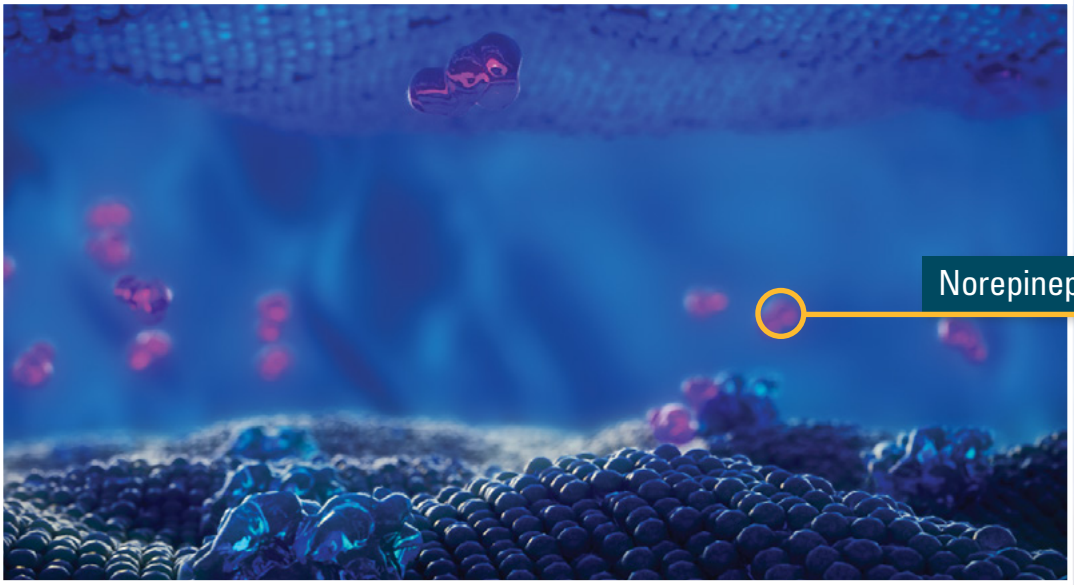


…the need for a higher dose of opioids to obtain a response[3]

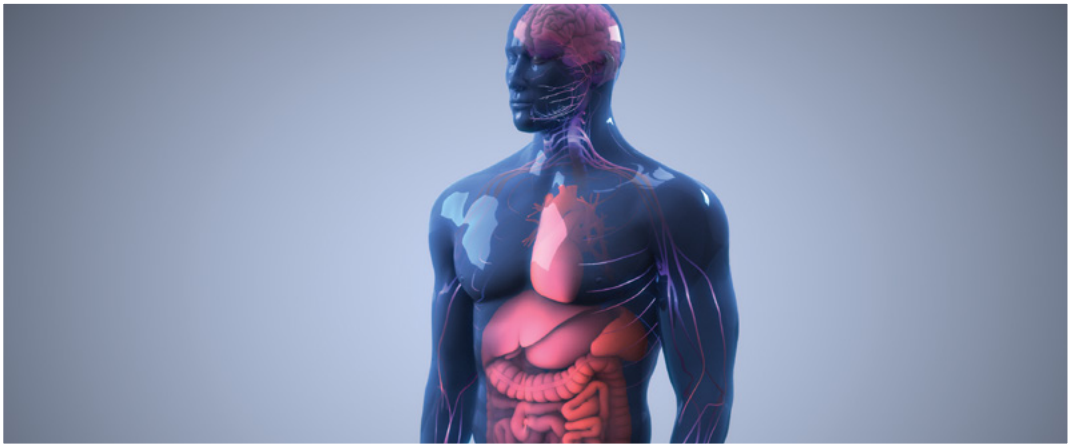
- Over time, repeated exposure to escalating doses of opioid drugs diminishes the responsiveness of the opioid receptors, producing tolerance[3]
- When tolerance develops, the user needs greater doses of opioid drugs to produce comparable feelings of pleasure[3]
- Physical dependence is characterized by developing tolerance to a substance and exhibiting withdrawal upon discontinuation[3]

The impact of withdrawal

Excessive release of norepinephrine leads to…



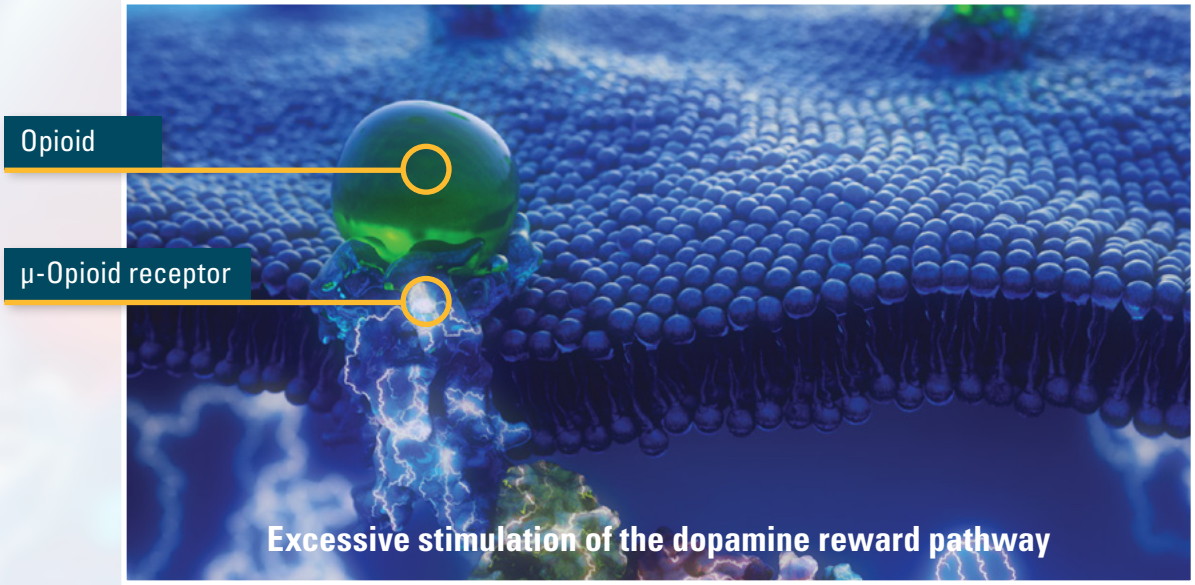
…withdrawal symptoms[3]



- When an individual develops physical dependence, the brain strives to counterbalance the sedative effects of opioids with elevated excitatory neurotransmitters, such as norepinephrine[3]
- The brain now depends on elevated opioid levels to function normally[3]
- During withdrawal, when no opioids are present, the excessive release of norepinephrine persists[3]
- This excessive norepinephrine release is partially responsible for the symptoms of withdrawal, such as[3]
  - Muscle cramps
  - Anxiety
  - Diarrhea

Full opioid agonists as pharmacotherapy for opioid dependence

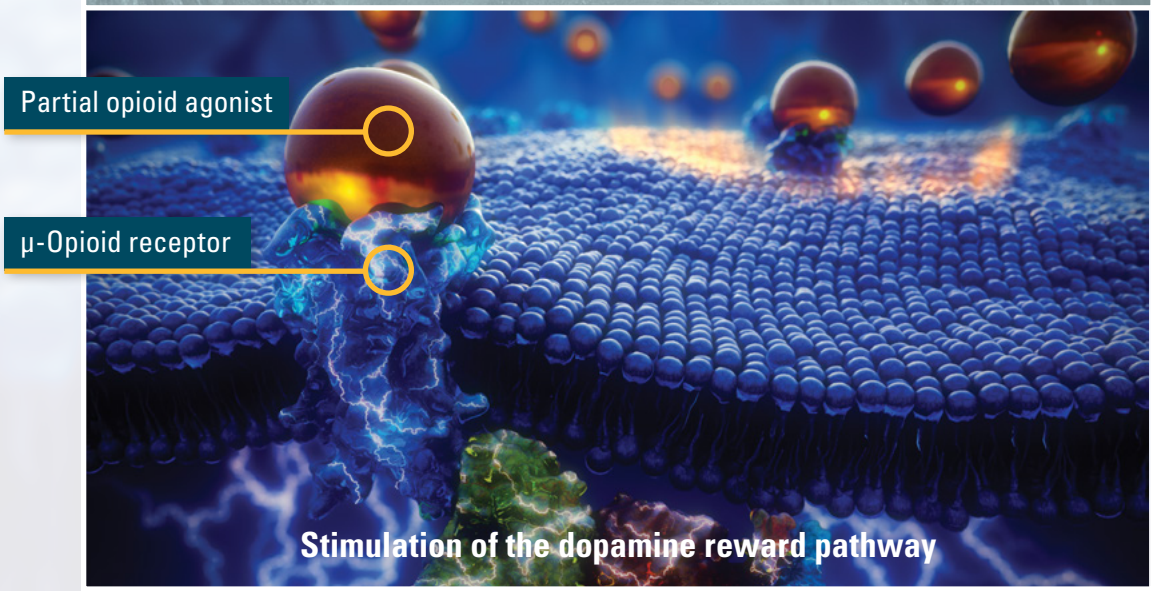
Full opioid agonists excessively stimulate the dopamine reward pathway



- Full opioid agonists attach to and activate opioid receptors in the same way as opioid drugs like heroin and oxycodone, triggering the brain's pleasure response[3,8]
- Treatment with full agonists does not require detoxification prior to treatment initiation but with chronic use can lead to dependence, tolerance, and subsequent withdrawal if discontinued[8]

Partial opioid agonists as pharmacotherapy for opioid dependence

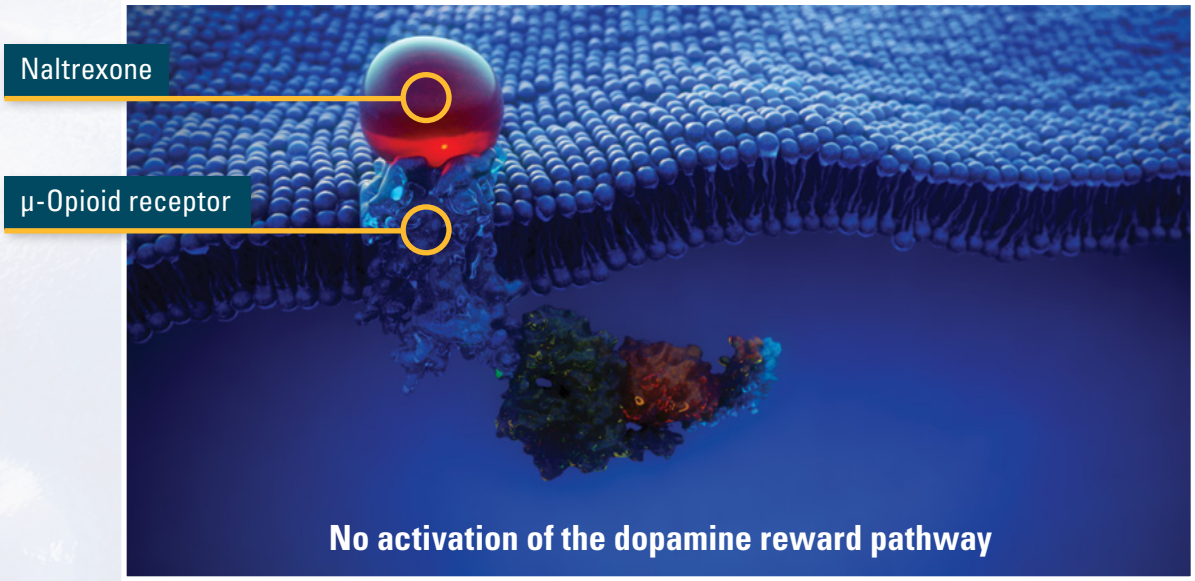
Partial opioid agonists stimulate the dopamine reward pathway



- Partial opioid agonists activate the μ-opioid receptors and stimulate the release of dopamine; however, partial agonists produce a more limited response than full agonists[9]
- With chronic use, partial agonists can lead to dependence and subsequent withdrawal if discontinued[10]
- Treatment with partial agonists does not require detoxification prior to the initiation of treatment[9]

Antagonist therapy for opioid dependence

Naltrexone binding to a μ-opioid receptor



- Naltrexone, the active ingredient in VIVITROL, is an opioid antagonist with highest binding affinity to μ-opioid receptors and does not stimulate the dopamine reward pathway[3,11]
- VIVITROL is not addictive and does not lead to physical dependence or withdrawal if VIVITROL treatment is discontinued[11]
- Prior to initiating VIVITROL, an opioid-free duration of a minimum of 7-10 days is recommended for patients, to avoid precipitation of opioid withdrawal that may be severe enough to require hospitalization[11]

Important Safety Information

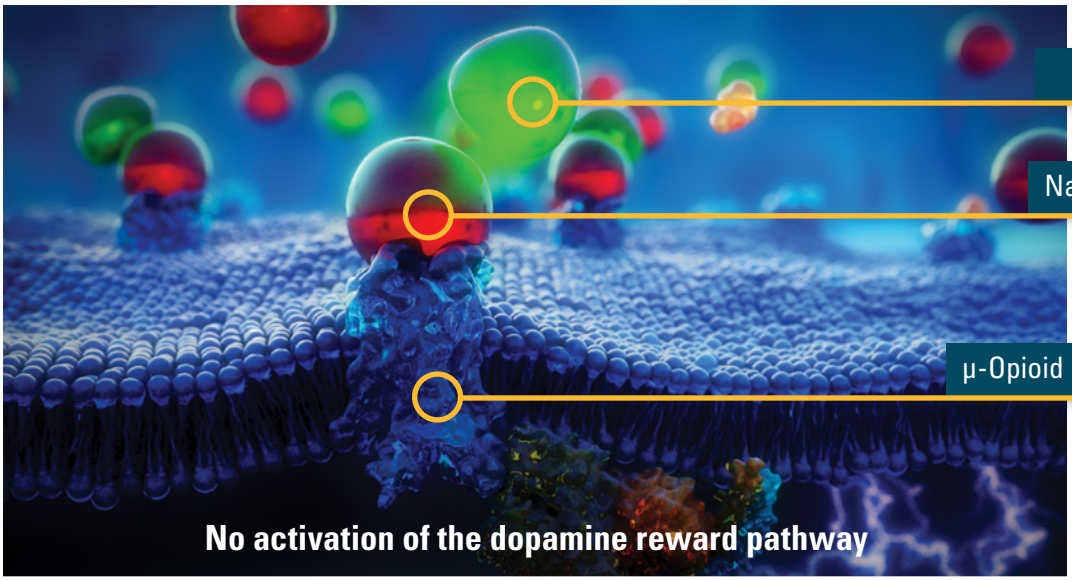
Contraindications

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

VIVITROL® creates an opioid blockade

VIVITROL blocks opioids from binding to the μ-opioid receptor[11]



- VIVITROL binds competitively with highest affinity to μ-opioid receptors producing an opioid agonist blockade[11]
- While reversible, the blockade prevents the subjective effects of opioid drugs such as euphoria[11]
- This blockade in combination with psychosocial therapy is thought to contribute to the prevention of relapse to opioid dependence[11]

Important Safety Information

Warning/Precaution

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.

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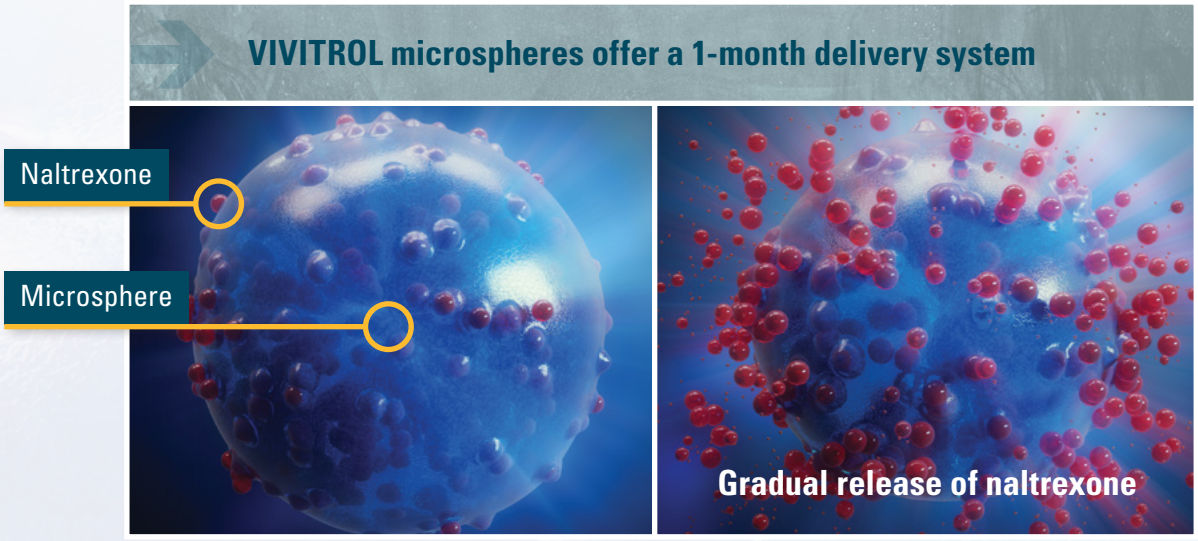
VIVITROL®: microsphere technology



VIVITROL produces a 1-month opioid blockade

- VIVITROL microspheres feature a 1-month delivery system[11]
- Naltrexone, the active component of VIVITROL, is embedded on and throughout microspheres[11,12]
- The microspheres are designed to break down over time and gradually release naltrexone in therapeutic concentrations over a 1-month period[11,12]

Important Safety Information

Warnings/Precautions

Vulnerability to Opioid Overdose (*continued*)

- Patients and caregivers should be told of this increased sensitivity to opioids and the risk of overdose.
- 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.

Characteristics of VIVITROL®

VIVITROL is[11]

- Nonaddictive and nonnarcotic
- A competitive opioid blocker (ie, antagonist)
- One month of naltrexone therapy in a single shot
- Used in conjunction with psychosocial therapy

VIVITROL is NOT[11]

- Pleasure-producing
- Associated with abuse
- A replacement or substitute for opioids
- Associated with withdrawal upon discontinuation of VIVITROL treatment
- A controlled substance

VIVITROL produces an opioid blockade

- By markedly attenuating or blocking, reversibly, the subjective effects of opioids, VIVITROL in combination with psychosocial therapy is thought to contribute to the prevention of relapse to opioid dependence[11]

Important Safety Information

Warning/Precaution

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, patients, including those being treated for alcohol dependence:
  - Should be opioid-free (including tramadol) for a minimum of 7–10 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.

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Vivitrol®
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Important Safety Information

Warnings/Precautions

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.

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 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 also include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache.

References: 1. National Institute on Drug Abuse. *Drugs, Brains, and Behavior: The Science of Addiction*. Bethesda, MD: National Institute on Drug Abuse, National Institutes of Health; 2010. NIH publication 10-5605. www.drugabuse.gov/sites/default/files/sciofaddiction.pdf. Accessed September 11, 2014. **2.** Fowler JS, Volkow ND, Kassed CA, Chang L. Imaging the addicted human brain. *Sci Pract Perspect*. 2007;3(2):4-16. **3.** Kosten TR, George TP. The neurobiology of opioid dependence: implications for treatment. *Sci Pract Perspect*. 2002;1(1):13-20. **4.** Leuenberger A. Endorphins, exercise and addictions: a review of exercise dependence. *Impulse*. 2006:1-9. http://impulse.appstate.edu/sites/impulse.appstate.edu/files/2006_06_05_Leuenberger.pdf. Accessed September 11, 2014. **5.** Spanagel R, Herz A, Shippenberg TS. Identification of the opioid receptor types mediating beta-endorphin-induced alterations in dopamine release in the nucleus accumbens. *Eur J Pharmacol*. 1990;190(1-2):177-184. **6.** Bressan RA, Crippa JA. The role of dopamine in reward and pleasure behavior – review of data from preclinical research. *Acta Psychiatr Scand*. 2005;111(suppl 427):14-21. **7.** Mizoguchi H, Tseng LF, Suzuki T, Sora I, Narita M. Differential mechanism of G-protein activation induced by endogenous mu-opioid peptides, endomorphin and beta-endorphin. *Jpn J Pharmacol*. 2002;89(3):229-234. **8.** Dolophine hydrochloride [prescribing information]. Roxane Laboratories, Inc. Columbus, OH; 2013. **9.** 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. (SAM) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2004. **10.** Suboxone sublingual film [full prescribing information]. Richmond, VA: Reckitt Benckiser Pharmaceuticals Inc; 2011. **11.** VIVITROL [prescribing information]. Waltham, MA: Alkermes, Inc; 2013. **12.** Dean RL. The preclinical development of Medisorb naltrexone, a once a month long-acting injection, for the treatment of alcohol dependence. *Front Biosci*. 2005;10:643-655.

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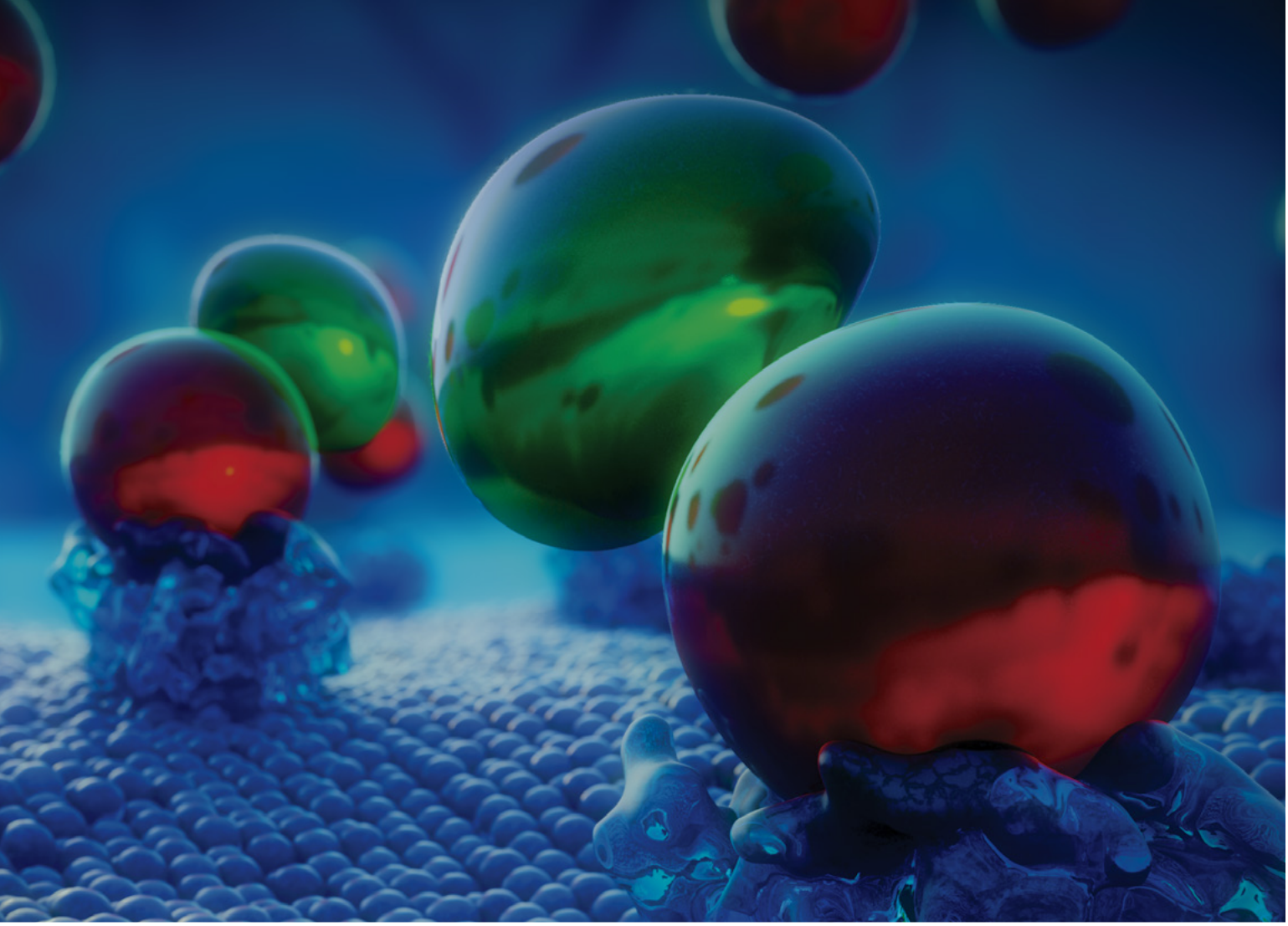

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