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Injectable Extended-Release Naltrexone to Treat Opioid Use Disorder

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CADTH

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Summary

- Vivitrol is an extended-release injectable formulation of naltrexone, administered as an intramuscular injection once a month. Naltrexone is an opioid-receptor antagonist that blocks the euphoric effects of opioids. Unlike other treatments for opioid use disorder, including buprenorphine/naloxone and methadone, naltrexone is not associated with the development of tolerance and dependence, and lacks the potential for misuse and diversion. However, because the oral formulation requires a daily dosage, poor adherence to the medication has limited its efficacy for the prevention of relapse in patients with opioid use disorder. The extended-release injectable formulation of naltrexone was developed to improve treatment adherence and retention.

- Vivitrol has not received marketing approval in Canada and is available only for research purposes or through Health Canada's Special Access Programme for the treatment of opioid use disorder or alcohol use disorder. In October 2010, the US FDA approved Vivitrol for the prevention of relapse to opioid dependence following opioid detoxification. Before starting Vivitrol, an opioid-free period of a minimum of seven to 10 days is recommended to avoid precipitating withdrawal, symptoms of which may be severe enough to require hospitalization. There are currently no recommendations to guide the duration of treatment with Vivitrol.

- Results from one phase III, randomized, placebo-controlled, double-blind trial in patients with opioid use disorder who had recently undergone detoxification showed Vivitrol to be superior to placebo for improving abstinence and treatment retention, as well as for reducing opioid cravings over a six-month treatment period. Approximately one-half of patients who received Vivitrol for an additional year in an open-label extension study remained abstinent from opioids.

- Preliminary evidence from phase III trials and studies in real-world clinical settings demonstrates that Vivitrol may be beneficial for preventing relapse in two subpopulations: people living within the corrections system and people living with HIV.

- None of the phase III trials reported deaths due to overdose in patients receiving Vivitrol. The majority of commonly reported adverse effects, including nasopharyngitis (cold symptoms), insomnia, hypertension, influenza, and injection-site pain, were mild or moderate. Abnormal liver function test results occurred primarily in patients with existing hepatitis C infection, but were transient and not clinically significant. Severe injection-site reactions were noted in some patients.

- There are several clinical challenges and knowledge gaps associated with the initiation, long-term use, and role of Vivitrol relative to other treatments for opioid use disorder. These will need to be addressed when considering adopting Vivitrol in clinical practice. They include the approach to transitioning patients from other treatments (including methadone or buprenorphine/naloxone) to treatment with Vivitrol, pain management, duration of treatment, long-term risk of relapse and opioid overdose, efficacy and cost compared with other therapies

for opioid use disorder, and use in certain subpopulations. When considering adopting Vivitrol in clinical practice, the requirement for total abstinence from opioids for seven to 10 days before initiating treatment may present a challenge.

- A Risk Evaluation and Mitigation Strategy, consisting of directions for proper injection technique and patient counselling materials, is in place in the US to inform health care providers and patients about the potentially serious risks associated with the use of Vivitrol, including severe injection-site reactions, sudden opioid withdrawal during treatment initiation, vulnerability to opioid overdose, and hepatotoxicity (drug-induced liver damage).

Background

Opioid use disorder (also known as opioid dependence), defined as a problematic pattern of opioid use leading to clinically significant impairment or distress, is a growing public health concern in Canada associated with significant morbidity and mortality.[1-3] Individuals with opioid use disorder are at greater risk for incarceration, blood-borne infections, and fatal overdose.[4] In addition, babies born to mothers who used opioids during pregnancy are at increased risk for neonatal abstinence syndrome, a condition that can be life-threatening if not promptly recognized and treated.[5] While heroin has historically been the most commonly misused opioid, non-medical use of prescription opioid analgesics (such as morphine, oxycodone, hydromorphone, and fentanyl) is now the dominant form of opioid misuse.[6] "Misuse" has been defined as "the intentional or unintentional use of a prescribed medication in a manner that is contrary to directions, regardless of whether a harmful outcome occurs."[7]

Canada is the world's second largest per-capita consumer of prescription opioids.[8] A total of 3.8 million Canadians more than 15 years of age (representing 13% of the total population) reported using opioid pain relievers in the past year, according to a Statistics Canada survey conducted in 2015.[9] Among users of opioid pain relievers, 2.0% (83,000 Canadians, representing 0.3% of the total population) reported misusing them. A joint report by the Canadian Institute for Health Information and the Canadian Centre on Substance Abuse found that, between 2007-2008 and 2014-2015, the rate of hospitalizations due to opioid poisoning in Canada increased by more than 30%.[10] Results from the report showed that opioid poisoning results in more than 13 hospitalizations per day in Canada, with an average length of stay of eight days. The report also found that the rate of emergency department visits due to opioid poisoning increased by 53% in Alberta and by 22% in Ontario between 2010-2011 and 2014-2015. The number of people enrolled in methadone maintenance treatment programs in Ontario increased from approximately 7,800 in 2001 to more than 35,000 in 2011.[11] Available preliminary data from all the provinces and territories (excluding Quebec) from 2016 indicate that there were 2,458 apparent opioid-related deaths in Canada.[12] The significant burden of opioid misuse on the Canadian health care system has triggered multi-pronged efforts in various jurisdictions to identify key factors contributing to the epidemic, as well as to address the unmet treatment needs of patients with opioid use disorder.[13]

Current guidelines recommend maintenance therapy with buprenorphine/naloxone or methadone for the treatment of patients with opioid use disorder.[2] When taken as prescribed, these medications alleviate withdrawal symptoms and diminish cravings without the typical euphoric effects of opioids.[2] However, both medications are considered controlled substances that carry certain prescribing and dispensing restrictions, depending on the jurisdiction, which limits accessibility, particularly in remote settings.[1,2,14-16] Currently available formulations of both buprenorphine/naloxone and methadone require daily supervised administration early in treatment or daily self-administration once the patient is clinically stable.[17] Thus, particularly in an office-based treatment setting where medication administration is unsupervised, effectiveness relies on long-term patient adherence to daily treatment, and there is a risk of diversion, misuse, and overdose.[17] Furthermore, there is also a risk of accidental pediatric exposure. The US Centers for Disease Control and Prevention reported that, between 2010 and 2011, 9.5% of emergency hospitalizations for drug ingestion among children younger than six years of age were caused by buprenorphine/naloxone.[18]

Oral naltrexone (Revia or its generic equivalents) is available in Canada as an alternative to buprenorphine/naloxone or methadone for treatment of opioid use disorder.[19] Naltrexone is an opioid-receptor antagonist that blocks the euphoric effects of opioids.[20] Potential benefits of naltrexone over buprenorphine/naloxone or methadone include few known drug–drug interactions; greater accessibility; lack of development of physical tolerance during long-term treatment; and lack of potential for dependence, misuse, and diversion.[2,21] However, because the oral formulation requires daily dosage, poor medication adherence has limited its efficacy for the prevention of relapse in patients with opioid use disorder.[2] An additional barrier to use is the requirement for total abstinence from opioids before starting treatment with naltrexone.

These limitations in currently available treatment options for opioid use disorder in Canada have spurred interest in alternative formulations.

The Technology

Vivitrol (Alkermes, Inc., Waltham, Massachusetts) is an extended-release injectable formulation of naltrexone.[22] It is administered by a health care professional as an intramuscular injection into the gluteal muscle.[23] Naltrexone is encapsulated in microspheres made of a biodegradable polymer and continuously released over one month at a set dose of 380 mg per injection.[22] In the US, the extended-release injectable formulation was first approved for patients with alcohol use disorder. It was later used to improve treatment adherence and retention in comparison with oral naltrexone in patients with opioid use disorder. Before initiating Vivitrol, an opioid-free period of at least seven to 10 days is recommended to avoid precipitating withdrawal, which may be severe enough to require hospitalization.[23] A Risk Evaluation and Mitigation Strategy, consisting of directions for proper injection technique and patient counselling materials, is in place in the US to inform health care providers and patients about the potentially serious risks associated with the use of Vivitrol, including severe injection-site reactions, sudden opioid withdrawal during treatment initiation, vulnerability to opioid overdose, and hepatotoxicity.[24] To prevent severe injection-site reactions, Vivitrol must not be given intravenously, subcutaneously, or into adipose (fat) tissue. Customized needles of two different lengths are provided with the medication. The proper needle, based on body build, should be selected. Vivitrol must not be injected with any other needle. It is also recommended that the medication be administered on alternating sides of the patient for each subsequent injection.[24] There are currently no recommendations to guide the duration of treatment with Vivitrol.[25]

Regulatory Status

Vivitrol has not received marketing approval in Canada, and it is not known whether a submission to Health Canada is planned. Vivitrol is available in Canada only for research purposes or through Health Canada's Special Access Programme for the treatment of opioid use disorder or alcohol use disorder.[2] In October 2010, the US FDA approved Vivitrol for the prevention of relapse to opioid dependence following opioid detoxification,[26] and the drug is indicated as part of a comprehensive management program that includes psychosocial support. The FDA has also approved Vivitrol for the treatment of alcohol use disorder in patients who can abstain from alcohol in an outpatient setting before starting treatment.[26]

Patient Group

Although the true prevalence of opioid use disorder in Canada is unknown, there are an estimated 75,000 to 125,000 injection-drug users (the vast majority of whom inject opioids such as heroin) and 200,000 people with prescription opioid use disorder.[27,28] The misuse of opioids leads to tolerance to the euphoric effects of the opioid, cravings for the drug, and a physiological withdrawal state when use is tapered quickly or stopped.[29] Opioid use disorder is characterized by the compulsive, prolonged administration of opioid substances despite the treatment of acute withdrawal.[3] As a result, individuals experience physical dependence, medical and psychological problems, and social dysfunction.[6] Opioid use disorder increases the risk of death, local and systemic infections (including cellulitis, endocarditis, osteomyelitis, tuberculosis, and pneumonia), infection with a blood-borne pathogen (such as HIV, hepatitis B, and hepatitis C), and narcotic bowel syndrome (an increase in abdominal pain associated with continued or escalating dosages of opioids).[4] Opioid users also have a higher rate of accident-related injuries compared with the general population.[4]

According to US prescribing information, the patient population approved by the FDA for Vivitrol is individuals who have undergone opioid detoxification and wish to prevent relapse.[23] Vivitrol may also be considered for those with concurrent opioid and alcohol abuse disorders, as this group is at even higher risk for opioid overdose.[30] There are currently no estimates of the number of patients who have received oral naltrexone following opioid detoxification in Canada. Data from Ontario Drug Benefit database records between April 2011 and March 2012 indicate that fewer than 1% of patients who were eligible for public coverage of naltrexone for alcohol use disorder received treatment, although it was not reported whether any of these patients had concomitant opioid use disorder.[31]

In the US, there has been interest in using Vivitrol in various subpopulations, since agonist therapy with buprenorphine/naloxone or methadone may be less suitable for certain patients, including young adults and adolescents; those with a brief history of opioid use disorder or who are new to treatment; those whose employment might prohibit opioid use (e.g., health care providers, pilots, police force, firefighters, and military personnel); and those who have achieved abstinence during in-patient or residential treatment or incarceration and are at risk of relapse after discharge.[25,32-35] There is some evidence from phase III clinical trials that Vivitrol may be beneficial in criminal justice settings and for those living with HIV (described in The Evidence section).[33,36,37]

Several ongoing phase III and IV trials are evaluating the effect of Vivitrol in opioid-dependent incarcerated offenders who are returning to the community.[38-42] Outcomes include relapse, treatment adherence, re-incarceration, injection-drug use, and HIV risk behaviours. One of these trials is specifically evaluating the clinical efficacy of Vivitrol for controlling viral load and preventing relapse in people living with HIV who are opioid-dependent and are prisoners or jail detainees.[41] One phase IV trial is assessing the feasibility of using Vivitrol in opioid-dependent individuals in drug-court settings that offer substance use treatment as a sentencing option in lieu of incarceration.[43] Outcome measures include the number of new arrests and incarcerations, and positive drug screens over a 12-month period. A phase IV ongoing, randomized, open-label trial is evaluating Vivitrol versus usual treatment with buprenorphine and psychosocial counselling in young adults and adolescents (aged 15 to 21 years) with opioid use disorder.[44] Outcomes include opioid use, treatment retention, and HIV risk behaviours at six months.

Current Practice

Opioid use disorder is a chronic, relapsing illness that requires long-term maintenance treatment.[2] Guidelines strongly recommend against withdrawal management alone (i.e., detoxification without transition to longer-term treatment), as this approach has been associated with elevated rates of relapse, transmission of infectious diseases, criminal activity, and an increased risk of death from overdose, following the loss of tolerance to the effects of opioids after complete discontinuation.[1,2,4] Maintenance treatment of opioid use disorder involves a comprehensive approach that combines approved pharmacological therapy with counselling, psychosocial rehabilitation, and other behavioural therapies to reduce opioid drug misuse by decreasing cravings, addressing withdrawal symptoms, and promoting functional recovery in everyday living.[2] Treatment goals focus on functional recovery rather than solely on abstinence outcomes. Long-term maintenance treatment for two years is recommended.[45-48] However, according to the clinical expert consulted for this bulletin, at least six months of complete abstinence from opioids should be achieved before any tapering of maintenance therapy is attempted (Dr. Peter Selby, Director, Medical Education, and Clinician Scientist, Addictions, Centre for Addiction and Mental Health, Toronto, ON: personal communication, 2017 Jun 26).The requirements for abstinence may vary in patients seeking transition to another pharmacotherapy for opioid use disorder.

Current guidelines recommend maintenance therapy with buprenorphine/naloxone as first-line treatment for opioid use disorder because of its potential advantages compared with methadone. These include a potentially improved safety profile, a lower risk of overdose or diversion, and the potential for more flexible at-home administration, or administration every second day.[2] Increasingly, provinces are removing the requirement for physicians to hold a methadone exemption before prescribing buprenorphine/naloxone.[15,16,49] Methadone may be considered first-line when there are contraindications to buprenorphine/naloxone or when a challenging induction is anticipated because of prior failures of buprenorphine/naloxone treatment, a history of severe withdrawal symptoms, or an anticipated need for high-dose maintenance treatment.[2] Because of its narrow therapeutic index in some patients, especially during the first few weeks of treatment, methadone can be prescribed only by physicians who hold a methadone exemption granted by Health

Canada.[1,14] Depending on the jurisdiction, for the first two to six months of therapy, methadone is dispensed for daily witnessed ingestion at specialized drug treatment clinics or pharmacies. This has proved to be a barrier for patients, especially those in rural communities.[1,50] Alternative approaches for patients with opioid use disorder who respond poorly to other maintenance treatments include slow-release oral morphine and injectable diacetylmorphine (also known as heroin).[2] In September 2016, Health Canada amended regulations allowing doctors to prescribe diacetylmorphine under the Special Access Programme to individuals with severe opioid use disorder for whom other treatment approaches have repeatedly failed.[51]

Although naltrexone is not considered a controlled substance in Canada and has no special prescribing or dispensing requirements, the oral short-acting formulation is rarely used in clinical practice.[2] This is largely because patients are required to abstain completely from opioids for a minimum of seven to 10 days to avoid precipitating withdrawal and because poor adherence to the daily dosage results in a high rate of relapse.[2] Oral naltrexone may be considered for individuals who wish to avoid opioid-agonist treatment and who are highly motivated to stay abstinent, including individuals with occupations that may prohibit opioid-agonist treatment (including health care professionals, firefighters, and those who transport hazardous materials).[2] In this case, gradual opioid-agonist tapering (over more than one month) in a supervised outpatient or residential setting with transition to long-term addiction treatment is recommended over rapid (less than one week) opioid-agonist taper in an in-patient setting. For individuals with a successful and sustained response to opioid-agonist treatment, a slow tapering of therapy over 12 months, with transition to oral naltrexone upon cessation of opioids, may be considered.[2] Oral naltrexone should be prescribed only to patients who are engaged in ongoing addiction care and can be assessed regularly on follow-up for risk or signs of relapse to opioid use.

In the US, guidelines also recommend treatment with buprenorphine or methadone as first-line treatment options for opioid use disorder.[25,52] Vivitrol is considered when treatment with buprenorphine or methadone is contraindicated, unacceptable, unavailable, or discontinued, and when abstinence has been achieved for a sufficient period of time.[52] The guidelines state that there is insufficient evidence for the efficacy of oral naltrexone and that it should be reserved for patients in whom adherence can be supervised and monitored.[25,52] Psychosocial treatment is recommended in conjunction with Vivitrol treatment.[25] There are no recommendations for the duration of treatment, which may instead be based on clinical judgment and on the patient's individual circumstances.[25]

Methods

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, and the Cochrane Library. Grey literature was identified by searching relevant sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters). No methodological filters were applied. Where possible, retrieval was limited to the human population. The search was limited to English-language documents with no date limit applied. Regular alerts updated the search until project completion; only citations retrieved before May 25, 2017 were incorporated into the analysis. Conference abstracts were excluded from the search results. Published phase III randomized controlled trials reporting the clinical efficacy and safety of the FDA-approved formulation of extended-release injectable naltrexone (Vivitrol) for the treatment of opioid use disorder were selected for inclusion in The Evidence and Adverse Event sections of this bulletin. Studies reporting the effect of Vivitrol on patient outcomes in real-world clinical settings were also included in The Evidence section. An open-label extension study of one of the selected phase III trials evaluating the long-term safety of Vivitrol was also included in the Adverse Event section. Meta-analyses, case reports, editorials, letters, and narrative literature reviews were excluded.

The Evidence

Four phase III trials evaluated the efficacy of Vivitrol for the prevention of relapse in patients with opioid use disorder.[32,33,36,37] Details of these trials are summarized in Table 1. One of the trials served as a pivotal trial for regulatory approval in the US.[32] An open-label extension study of the pivotal trial evaluated the safety and efficacy of Vivitrol over one year following completion of the pivotal trial.[53] In addition, three studies have reported the effect of Vivitrol on patient outcomes in real-world clinical settings.[54-56]

Table 1: Summary of Vivitrol Phase III Efficacy Trials

Study	Main Inclusion/Exclusion Criteria	Study Details	Baseline Characteristics
ALK21-013, 2011[32] N = 250 (Pivotal trial)	**Inclusion:** • Adult (more than 18 years of age) • Meeting DSM-IV diagnostic criteria for opioid dependence disorder • Completing in-patient opioid detoxification (≤30 days) and off opioids for at least 7 days • Voluntarily seeking treatment **Exclusion:** • Offenders • AIDS • Significant medical conditions (e.g., acute renal failure, hepatic failure, active hepatitis, endocarditis, tuberculosis) • Positive naloxone challenge (increases in vital signs or opioid withdrawal symptoms) • Psychosis, bipolar disorder, major depressive disorder with suicidal ideation • Dependence within prior year to any drugs other than prescription opioids or heroin, caffeine, marijuana, or nicotine • Current alcohol dependence • Positive urine test for cocaine or amphetamines • Naltrexone use within past 6 months • Pregnancy or breastfeeding	**Design:** Multi-centre, randomized, placebo-controlled, double-blind **Intervention:** 380 mg Vivitrol every 4 weeks **Comparator:** Placebo injection every 4 weeks **Setting:** 13 clinical sites in Russia **Duration:** 24 weeks	**Mean age, years:** 29.4 to 29.7 **Caucasian, N (%):** 248 (99.2) **Male, N (%):** 220 (88.0%) **HIV serology positive, N (%):** 103 (41.2) **Hepatitis C positive, N (%):** 228 (91.2) **Primary opioid of misuse, N (%):** Heroin 221 (88.4) **Mean duration of opioid dependence, years:** 9.1 to 10.0 **Mean duration of pre-study, in-patient detoxification days:** 18

Study	Main Inclusion/Exclusion Criteria	Study Details	Baseline Characteristics
Lee et al., 2015[37] N = 34 (Special population)	**Inclusion:** • Adult (more than 18 years of age) • Meeting DSM-IV diagnostic criteria for current opioid dependence • Currently incarcerated with a known release date • Not currently on or intending to access methadone or buprenorphine treatment • Opioid-free by self-report and opioid-negative urine toxicology at randomization **Exclusion:** • Serious uncontrolled medical or psychiatric illness • Liver function tests > 3 times upper limit of normal • Chronic pain requiring opioid treatment • Pregnancy	**Design:** Randomized, open-label, pilot **Intervention:** 380 mg Vivitrol every 4 weeks **Comparator:** Treatment as usual **Setting:** New York City jails and Bellevue Hospital Center **Duration:** 8 weeks	**Mean age, years:** 40 to 47 **Male, N (%):** 33 (100.0%) **Opioid use, 7 days pre-arrest, N (%):** Heroin 32 (97.0) Cocaine 21 (63.6) Prescription opioids 5 (15.2)
Lee et al., 2016[33] N = 308 (Special population)	**Inclusion:** • Meeting DSM-IV diagnostic criteria for current or previous opioid dependence • Adult (18 to 60 years of age) • Preference for opiate-free rather than opioid-agonist therapy • Opioid-free status confirmed by negative urine screening • Residence in community • Receipt of adjudicated sentence that included supervision (parole, probation, outpatient drug-court programs, or other court-mandated treatment) or release from jail or plea-bargain arrangement in the previous 12 months **Exclusion:** • Drug or alcohol dependence that would require a level of care that would interfere with trial participation • Untreated psychiatric disorder or medical condition (including liver enzyme levels > 3 times upper limit of normal, BMI > 40) • Chronic pain requiring opioids • Drug overdose in previous 3 years requiring hospitalization • Pregnancy or lactation	**Design:** Multi-centre, randomized, open-label **Intervention:** 380 mg Vivitrol every 4 weeks **Comparator:** Treatment as usual **Setting:** 5 independently funded research sites **Duration:** 24 weeks	**Mean age, years:** 44.4 to 43.2 **Male, N (%):** 261 (84.7%) **Race or ethnic group, N (%):** Black 155 (50.3) White 61 (19.8) Hispanic 82 (26.6) **Primary opioid of misuse (lifetime), N (%):** Heroin 272 (88.3) **Needing opioid detoxification to enter trial, N (%):** 27 (8.8)

Study	Main Inclusion/Exclusion Criteria	Study Details	Baseline Characteristics
CTN-0055 CHOICES[36] N = 51 (Special population)	**Inclusion:** • Adult (more than 18 years of age) • Meeting DSM-5 diagnostic criteria for moderate or severe opioid or alcohol use disorder • Initiating or continuing HIV care at the site • Initiating or continuing ART, regardless of CD4 count **Exclusion:** • Disabling or terminal medical illness • AST or ALT elevations > 5 times the upper limit of normal • Prothrombin time with INR > 1.5 or platelet count < 100,000 • Anticipated surgery during study participation • Chronic pain requiring ongoing opioid analgesics • Received methadone or buprenorphine maintenance therapy in past 4 weeks • Received Vivitrol for opioid or alcohol use disorder in past 3 months • Pending legal action • Pregnancy or breastfeeding	**Design:** Multi-centre, randomized, open-label, pilot **Intervention:** 380 mg Vivitrol every 4 weeks **Comparator:** Treatment as usual primarily with office-based buprenorphine/naloxone (84%) **Setting:** Two outpatient HIV clinics in Vancouver and Chicago **Duration:** 16 weeks	**Mean age, years (SD):** 46 (10) **Race or ethnic group, N (%):** Black/ African American 24 (47.1) White 13 (25.5) Other 14 (27.5) **Male, N (%):** 29 (56.9%) **HIV serology positive, N (%):** 51 (100) **Substance use disorder, N (%):** Opioid alone 16 (31.4) Alcohol alone 27 (52.9) Opioid and alcohol 8 (15.7)

ART = antiretroviral therapy; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition); DSM-5 = Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition); INR = international normalized ratio.

Pivotal Placebo-Controlled Trial and Open-Label Extension Study

Approval of Vivitrol in the US was based on results of a randomized, placebo-controlled, double-blind trial (ALK21-013) designed to evaluate Vivitrol over six months in patients voluntarily seeking treatment for opioid use disorder.[32] The trial was conducted in Russia, where maintenance therapy with methadone or buprenorphine/naloxone is prohibited by law. A total of 250 patients were randomized to receive Vivitrol (n = 126) or placebo injection (n = 124) within one week following detoxification and then every four weeks thereafter. Participants also received biweekly sessions of individual drug counselling.

Efficacy outcomes were based on the intention-to-treat population, consisting of all randomized patients who received study medication and provided efficacy data. The primary outcome was the response profile for confirmed abstinence (defined by negative urine testing for opioids and no self-reported opioid use), calculated as the number of confirmed abstinence weeks divided by the number of scheduled tests during weeks 5 to 24. The investigators prospectively omitted weeks 1 to 4 from the primary outcome to allow time for participants to engage in treatment and to acknowledge that some may challenge the opioid blockade early in treatment. All missing urine drug-test results were imputed as positive for opioids. Secondary outcomes were self-reported opioid-free days, opioid craving scores, number of days of treatment

retention, and relapse to physiological opioid dependence (tested by naloxone challenge upon any positive urine drug screen, upon treatment discontinuation, or at week 24).

More patients in the Vivitrol group completed the study (53.2% versus 37.9% with placebo). The most common reason for discontinuation in both arms was a lack of efficacy (17.5% in the Vivitrol group versus 27.4% in the placebo group). Results showed that Vivitrol increased the proportion of opioid-free weeks compared with the placebo group (90.0% with Vivitrol versus 35.0% with placebo; treatment difference 55.0%; 95% confidence interval (CI), 15.9% to 76.1%, *P* = 0.0002). Vivitrol also increased the proportion of participants with total confirmed abstinence compared with placebo (35.7% with Vivitrol versus 22.6% with placebo; treatment difference 1.58; 95% CI, 1.06 to 2.36, *P* = 0.0224). When efficacy was analyzed based on the full 24-week period, results were still significant (*P* = 0.0001). Statistically significant differences were also observed for all secondary outcomes, including self-reported opioid-free days, opioid craving scores, number of days of treatment retention, and relapse to physiological opioid dependence.

Upon completion of the 24-week double-blind phase, participants (n = 114) entered an open-label extension study to assess longer-term retention, durability of effect, and safety over an additional year of treatment with Vivitrol.[53] Sixty-seven patients continued to receive treatment with Vivitrol, and patients receiving placebo during the double-blind treatment period (n = 47) were switched to Vivitrol. All patients also received monthly drug counselling sessions. Overall, 62.3% (95% CI, 52.7% to 71.2%) completed the extension. Of the participants originally randomized to receive Vivitrol during the double-blind treatment phase, 31% (95% CI, 23.0% to 39.8%) maintained 18 months of treatment. The most common reason for discontinuation was withdrawal of consent. Two patients discontinued due to lack of efficacy. Urine testing showed that 50.9% (95% CI, 41.5% to 60.4%) of patients were abstinent from opioids during the one-year open-label phase.

The generalizability of the results from the pivotal trial and extension study is limited by the demographic characteristics of participants (i.e., most participants were young, white men who had been addicted to heroin for approximately 10 years). Individuals with significant medical or psychiatric conditions, and those who were pregnant or lactating, were excluded. Hence, similar results cannot be assumed for all individuals with opioid use disorder. In addition, the demographic, societal, and treatment system differences in different countries may affect the ability to extrapolate these findings to the Canadian health care setting.

Randomized Controlled Trials in Special Populations

The feasibility of using Vivitrol to prevent relapse to opioids following release from incarceration among opioid-dependent male adults was investigated in a proof-of-concept, open-label, randomized trial.[37] Participants were randomized to Vivitrol (n = 17) within one week before release from incarceration or usual treatment (brief counselling and referrals to community addiction treatment services) (n = 17). One participant in the Vivitrol group was never released and was excluded from the primary analysis. At the four-week follow-up, there was a significant difference in the primary outcome of opioid relapse (defined as more than 10 days of opioid misuse in a 28-day period by self-report and more than two urine test results that are positive for opioids). Six (38%) participants in the Vivitrol group compared with 15 (88%) participants in the control group relapsed (*P* < 0.004; odds ratio [OR] 0.08; 95% CI, 0.01 to 0.48). There were no significant differences between groups in the secondary outcomes of post-release injection-drug use, HIV risk behaviours, cocaine use, participation in community drug treatment, or re-incarceration.

The efficacy of a 24-week course of Vivitrol for the prevention of relapse among adult community-dwelling offenders who had a history of opioid use disorder but who were abstinent from opioids was evaluated in a randomized, open-label trial.[33] The primary outcome was the time to an opioid-relapse event (defined as more than 10 days of opioid misuse in a 28-day period as assessed by self-report or by testing of urine samples obtained every two weeks). A positive or missing sample was computed as five days of opioid use. Participants were randomized to Vivitrol (n = 153) or usual treatment (consisting of brief counselling and referrals for community treatment programs) (n = 155). Vivitrol was discontinued at the end of the 24-week treatment phase. If preferred or indicated during the trial and after the treatment phase, all participants were encouraged to access community treatment for relapse prevention, including buprenorphine or methadone. There was a post-treatment follow-up to week 78. Notably, all participants were financially compensated for attendance at individual visits.

During the 24-week treatment phase, participants assigned to Vivitrol had a longer median time to relapse than those assigned to usual treatment (10.5 versus 5.0 weeks, $P < 0.001$; hazard ratio 0.49; 95% CI, 0.36 to 0.68), a lower rate of relapse (43% versus 64% participants, $P < 0.001$; OR 0.43; 95% CI, 0.28 to 0.65), and a higher rate of opioid-negative urine samples (74% versus 56%, $P < 0.001$; OR 2.30; 95% CI, 1.48 to 3.54). At week 78 (approximately one year after the end of the treatment phase), rates of urine samples that were negative for opioids were equal (46% in each group, $P = 0.91$). The rates of other secondary outcome measures (including self-reported cocaine, alcohol, and intravenous drug use; HIV risk behaviours; and re-incarceration) did not differ significantly between treatment groups. More participants in the usual-treatment group pursued opioid-agonist treatments during the trial (37% versus 11% for the Vivitrol group; $P < 0.001$), primarily after resuming opioid misuse and relapse. No participants continued Vivitrol after the 24-week treatment phase. It is important to note that the drug had just been approved at the time of the trial and was not yet widely available.

CTN-055 CHOICES was an open-label, randomized pilot trial designed to assess the feasibility of Vivitrol for the treatment of opioid and/or alcohol use disorder in HIV clinics.[36] Fifty-one patients with HIV infection were randomly assigned to Vivitrol (n = 25) or usual treatment (the local standard of care for alcohol or opioid use disorder) (n = 26). All participants were referred to local counselling resources and attended monthly medical management appointments with treatment providers. Among patients with opioid use disorder with or without concomitant alcohol use disorder (n = 24), 42% of participants assigned to Vivitrol started treatment within four weeks of randomization and 100% of those remained on treatment with Vivitrol at 16 weeks. The main reason for not starting therapy with Vivitrol was inability to tolerate opioid detoxification. Although 100% of participants in the usual-treatment group initiated treatment within four weeks of randomization, only 50% remained on medication at 16 weeks. Similarly, retention in counselling at 16 weeks was higher in participants treated with Vivitrol (100% versus 40% with usual treatment). Although the trial was not powered for hypothesis testing of substance use or HIV treatment outcomes, secondary analyses suggested decreased use of opioids and improved viral suppression. Mean days of opioid use in the previous 30 days decreased from 17.3 to 4.1 for usual treatment and from 20.3 to 7.7 for Vivitrol. Among those with opioid use disorder, HIV viral suppression increased from 67% to 80% for Vivitrol and from 58% to 75% for usual treatment.[36]

Real-World Clinical Setting Studies

Two studies compared the naturalistic outcomes of treatment with Vivitrol relative to buprenorphine/naloxone or to psychosocial interventions alone in individuals with opioid disorder; these studies used outcome data collected and analyzed from the Missouri Department of Mental Health's Division of Behavioural Health.[54,55] These data were obtained from the Substance Abuse and Mental Health Services Administration Data Set. Methadone is administered in a separate program, and therefore was not included in the analyses. In the first study, data were analyzed from patients with opioid use disorder (N = 8,996) who were admitted and discharged during 2010-2011.[54] A composite outcome was created by summing four binary measures (abstinence, employment, arrests, and self-help meeting attendance). Results showed that patients receiving Vivitrol stayed in treatment longer, but did not show more benefit on composite outcomes than those receiving psychosocial treatment alone. Exploratory analyses suggested that patients receiving Vivitrol had better composite outcomes compared with those receiving oral naltrexone and buprenorphine/naloxone. The investigators concluded that these hypothesis-generating findings need to be further investigated in randomized clinical trials. In the second study, the effect of Vivitrol was assessed in individuals who were under community supervision (i.e., on parole or probation) by the state correctional agency, who received outpatient treatment for opioid use disorder and were followed during the 2013 fiscal year.[55] The primary statistical analysis consisted of a propensity score–adjusted logistic regression model for each outcome measure (abstinence, employment, arrests, and self-help meeting attendance). Results in patients with opioid use disorder showed that patients receiving Vivitrol had longer durations of care (97 days for those receiving Vivitrol [n =136] versus 63 days for those receiving oral naltrexone [n = 34], 69 days for those receiving buprenorphine/naloxone [n = 163], and 63 days for those receiving psychosocial intervention only [n = 866]). Patients receiving Vivitrol (n = 58) were more likely to achieve abstinence at discharge than patients receiving buprenorphine/naloxone (n = 68) (OR 6.35; 95% CI, 2.82 to 14.28; $P < 0.0001$), and than patients receiving psychosocial intervention alone (n = 484) (OR 2.60; 95%CI, 1.41 to 4.80; $P = 0.0022$). There was also a trend for patients receiving Vivitrol to achieve abstinence at discharge more frequently than patients receiving oral naltrexone (n = 15) (OR 3.15; 95% CI, 0.91 to 10.84; $P = 0.069$). No differences were found in employment or arrests in the relatively short time frame.

Current guidelines recommend that patients be in residential care settings when treatment with Vivitrol is started, because of the time required for detoxification.[2] The effect of therapy with Vivitrol on short-term outcomes among patients with opioid use disorder in residential rehabilitation programs was reported using a retrospective review of electronic records (N = 7,687) during 2011 from three residential detoxification and treatment facilities in Pennsylvania.[56] Rates of treatment completion and engagement in follow-up care in patients receiving Vivitrol were compared with a naturalistic control group of patients recommended for Vivitrol but who did not receive it. Overall, 598 (7.8%) patients were recommended for Vivitrol treatment and, of these, 168 (28.1%) received the treatment. It was not known what proportion of patients who received an initial injection of Vivitrol received subsequent injections or what the duration of treatment was. Compared with patients who were never treated with Vivitrol, patients receiving treatment were less likely to leave residential rehabilitation against medical advice (4.8% versus 30.2%; $P < 0.001$) and were more likely to attend their first post-discharge outpatient visit (37.7% versus 19.7%; $P < 0.001$). These differences remained significant after controlling for demographic variables.

Adverse Effects

Pivotal Placebo-Controlled Trial and Open-Label Extension Study

No overdose events, suicide attempts, or deaths were reported during the double-blind 24-week treatment phase of the pivotal trial or during the one-year open-label extension.[32,53] A greater proportion of individuals in the Vivitrol group experienced at least one adverse event (50.0% versus 32.3% with placebo), but no adverse events were judged to be severe. The most common adverse events (with a prevalence of more than 5%) in the Vivitrol group were nasopharyngitis, insomnia, hypertension, influenza, and injection-site pain. Injection-site pain was more prevalent in the Vivitrol group compared with the placebo group (5% versus 1%), although no cases of intractable pain were reported.[30] Two (2%) patients in each group discontinued treatment due to adverse events, but details of these events were not given. Abnormal results of liver function tests occurred more often in the Vivitrol group than in the placebo group (although differences were not statistically significant). Most cases of liver enzyme elevations greater than three times the upper limit of normal occurred in patients with existing hepatitis C infection.[57] There was no evidence of specific symptoms (such as jaundice, ascites, encephalopathy, or other signs of hepatic decompensation). Furthermore, in patients for whom subsequent data were available, enzyme elevations were transient and returned toward baseline levels despite continuing Vivitrol.[57] Three (2%) patients in the Vivitrol group reported serious adverse events of infectious etiology (two HIV-infected patients had symptoms suggesting progression to AIDS, and one patient had adnexitis). During the open-label extension study, injection-site reactions occurred in seven (6.1%) participants, but the majority were mild (three involved pain, two extravasation, one induration, and one swelling).[52] One participant with ongoing hepatitis B and C infections discontinued treatment owing to non-serious adverse event (elevations in liver enzymes). Four serious adverse events (acute pancreatitis, cardiomyopathy, hepatitis A, and pulmonary tuberculosis) were reported, and the pancreatitis was judged as possibly related to therapy with Vivitrol. Elevations in liver function tests occurred in 19 (16.7%) patients, but none of these elevations were clinically significant.[52]

Randomized Controlled Trials in Special Populations

None of the trials in special populations reported opioid overdoses in patients receiving Vivitrol.[32,33,36,37] In the larger multi-centre trial in community-dwelling adult offenders, the most common adverse events (with a prevalence of more than 5%) that occurred in Vivitrol group were injection-site reactions, headache, gastrointestinal upset, nasopharyngitis, and insomnia. Over the total 78 weeks observed, there were no overdose events in the Vivitrol group and seven in the usual-treatment group ($P = 0.02$).[33] Two trials reported severe injection-site reactions following treatment with Vivitrol (affecting four [2.6%] participants in the trial of community-dwelling offenders[33] and one [4%] participant in the trial in HIV clinics[36]).

Cost

The manufacturer's price for Vivitrol in Canada is currently unavailable, as the drug has not been approved for marketing.

In the US, the drug cost of Vivitrol is more than that for Probuphine (buprenorphine implant for subdermal administration, Braeburn Pharmaceuticals, Inc.), the only other long-acting non-oral treatment approved for opioid use disorder in the US (wholesale acquisition cost of US$1,309 per month

for Vivitrol versus US$825 per month for Probuphone).[58] At this wholesale acquisition cost, one month of treatment with Vivitrol costs more than maintenance treatment with generic buprenorphine sublingual tablets (US$278.63), Suboxone sublingual films (US$443.40), or generic buprenorphine/naloxone sublingual tablets (US$468.98).[59] Alkermes Inc. offers a co-pay savings program, which covers up to US$500 per month of co-pay or deductible expenses for eligible patients with a Vivitrol prescription.[60]

Concurrent Developments

The following section briefly describes some of the other long-acting treatment options for opioid use disorder that are in development.

Naltrexone Implants

Several types of implants, including Prodetoxon (Fidelity Capital, Moscow, Russia) and O'Neil Long-Acting Naltrexone Implant (Go Medical Industries Pty Ltd., Perth, Australia) have been developed for insertion, usually via a small incision, into the subcutaneous tissue of the lower abdominal wall.[61] These implants release a controlled amount of naltrexone into the circulation for three to six months, depending on the type of implant being used.[62,63] They have been used in rehabilitation centres throughout the US, the UK, Russia, and Australia.[62] Prodetoxon is the only implant that has received regulatory approval for use in Russia.[64,65] It contains 1,000 mg of naltrexone embedded in a matrix that is slowly released over two to three months.[64,66] The implant is biodegradable and does not require removal.[66] A systematic review found that naltrexone implants were superior to placebo implants (risk ratio [RR] 0.57; 95% CI, 0.48 to 0.68) and oral naltrexone (RR 0.57; 95% CI, 0.47 to 0.70) in suppressing opioid use.[67] No difference in opioid use (measured by urine testing or self-reports) was observed between patients using naltrexone implants and those on methadone maintenance (standardized mean difference −0.33; 95% CI, −0.93 to 0.26). This finding was based on low-quality evidence from a single study. There are two ongoing phase III trials comparing the effect of naltrexone implants with oral naltrexone on adherence to antiretroviral therapy[68] and on prevention of relapse to heroin addiction[69] in patients with opioid use disorder in Russia. An additional phase III trial is investigating the effect of a novel iGen/Atral-Cipan naltrexone implant versus oral naltrexone or placebo on abstinence, treatment retention, adherence, and cost-effectiveness during 12 weeks of treatment in opioid-dependent adults in the UK.[70] In July 2016, a US addiction treatment company (BioCorRx Inc., Anaheim, California) announced plans to pursue FDA approval for its naltrexone implant.[71]

Long-Acting Buprenorphine Formulations

Probuphine is a subdermal implant for the maintenance treatment of opioid use disorder, designed to provide continuous, non-fluctuating blood levels of buprenorphine for up to six months following a single outpatient office-based procedure.[72] In May 2016, the US FDA approved Probuphine implants for the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine-containing product (i.e., doses of no more than 8 mg per day of Subutex or Suboxone sublingual tablet or generic equivalent).[73,74] A submission to Health Canada for regulatory market approval is planned within 12 months (as of September 2016).[75] Results from two phase III, double-blind, placebo-controlled trials showed Probuphine to be superior to placebo implants in reducing illicit opioid use during a six-month treatment period in new entrants to therapy.[76,77] One phase III, double-blind, double-dummy, active-controlled trial showed Probuphine to be non-inferior to sublingual buprenorphine for the primary outcome of at least four of six months with no illicit opioid use among patients with opioid use disorder previously stabilized on a low-to-moderate dose (no more than 8 mg per day) of sublingual buprenorphine.[78] However, patients in all three trials required supplemental therapy with buprenorphine to manage symptoms of withdrawal, which could affect the ability of Probuphine to mitigate misuse and accidental pediatric exposure.[79] Three phase III trials and two open-label extension studies evaluating Probuphine for up to two six-month treatment cycles found the overall implant site adverse events to be comparable between treatment groups.[76-78,80,81] Commonly reported implant site adverse events, such as pain, pruritus, and erythema, were mild and resolved without treatment. There was no evidence of unscheduled or attempted implant removal, and there were no cases of implant migration. All US health care providers must complete a live training program on insertion and removal procedures, and become certified in the restricted Probuphine Risk Evaluation and Mitigation Strategy program before prescribing Probuphine or performing insertions and removals.[73]

RBP-6000 (Indivior PLC) is an investigational sustained-release monthly depot of buprenorphine for the treatment of opioid

use disorder.[82] After subcutaneous injection, the novel delivery system solidifies on contact with bodily fluids, forming a depot that releases buprenorphine continuously over one month. Positive preliminary results of a pivotal phase III clinical trial in new entrants to opioid use disorder therapy were released in August 2016.[82] This was a multi-centre, randomized, double-blind, placebo-controlled study, which randomized 489 patients with moderate or severe opioid use disorder to one of two dosage regimens of RBP-6000 or placebo. The primary objective of this study was to assess the efficacy of monthly subcutaneous injections of RBP-6000 in two dosage regimens: either 300 mg buprenorphine for six injections, or 300 mg for two injections followed by 100 mg buprenorphine for four injections, compared with placebo, during a six-month period in new entrants to medication-assisted treatment for opioid use disorder. Results showed that RBP-6000 achieved the primary outcome — the cumulative distribution function of the percentage of urine samples negative for opioids combined with self-reports of no illicit opioid use — collected from week 5 through week 24 ($P < 0.0001$ for both dosage regimens versus placebo). Safety results showed 2.8% of patients receiving RBP-6000 (both dosage regimens combined) experienced a serious treatment-emergent adverse event (TEAE) compared with 5.1% of patients on placebo. There were no related serious TEAEs across groups. Of patients receiving RBP-6000 (both dosage regimens combined), 7.2% experienced a severe TEAE compared with 4.0% of patients on placebo. Full results from the study, as well as the open-label extension to monitor safety in patients completing the double-blind trial, are expected in early 2017.

Two phase III clinical trials are being conducted to evaluate the long-term efficacy and safety of CAM2038 (Braeburn Pharmaceuticals and Camurus), two long-acting subcutaneous buprenorphine injections.[83,84] CAM2038 is being developed as once-weekly and once-monthly formulations that can be titrated to cover all phases of treatment, from initiation through maintenance, for opioid use disorder.[83,84] Both trials are evaluating the use of CAM2038 in new entrants to treatment as well as in patients who are currently receiving maintenance treatment with sublingual buprenorphine. The first randomized, double-blind, double-dummy, active-controlled phase III trial is designed to evaluate the non-inferiority of CAM2038 compared with sublingual buprenorphine/naloxone for initiation and maintenance treatment in 428 patients with moderate-to-severe opioid use disorder.[85] The primary outcome measure is treatment response, based on the percentage of urine samples negative for opioids combined with self-reports. Preliminary results show that CAM2038 achieved statistical non-inferiority compared with sublingual buprenorphine/naloxone for end points specified by both the FDA and the European Medicines Agency: responder rate (95% CI, −3.5% to 10.5%; $P < 0.001$) and percentage of urine samples negative for opioids (95% CI, 0.2% to 13.7%, $P < 0.001$).[86] CAM2038 also demonstrated statistical superiority over sublingual buprenorphine/naloxone for a secondary end point — cumulative distribution function of percentage of urine samples negative for opioids combined with self-reports — for weeks 5 to 24 ($P = 0.004$). The overall safety profiles were comparable between the two treatment groups, with few serious adverse events reported for CAM2038 (3.2%) or for sublingual buprenorphine/naloxone (6.0%). Injection-site reactions occurred in 19% of the CAM2038 patients versus 22% of those receiving buprenorphine/naloxone. Seventy-four per cent of injection-site reactions were reported as mild, 26% as moderate, and none was reported as severe. A second open-label 12-month trial will assess the safety and tolerability of CAM2038 once weekly and once monthly in 100 patients with opioid use disorder.[87] Results are anticipated in early 2017.

Implementation Issues

Opioid misuse poses a significant burden on patients, their families, communities, and the Canadian health care system. As a result, there are current intensified efforts to increase access to safe and effective treatment options for opioid use disorder by regulators, health care providers, and health advocates. In light of these trends, it is anticipated that, if the drug is approved, there might be significant interest in Vivitrol. A recent survey of a community-recruited cohort of individuals with opioid use disorder in Vancouver reported that 52.1% of participants were willing to try Vivitrol.[21] Although Vivitrol has been available in the US for several years, the rate of its adoption in routine clinical practice settings has been limited.[88,89] Several barriers to the use of Vivitrol have been noted, including high wholesale acquisition cost compared with currently available daily medications (including buprenorphine and methadone) or with the long-acting buprenorphine implant, lack of familiarity with its use, and perception of low patient demand (due, in part, to its mechanism of action as a pure opioid antagonist).The requirement for total abstinence from opioids for seven to 10 days before initiating treatment may also be a barrier for many patients.

There are also several clinical challenges and knowledge gaps associated with the initiation, long-term use, and role of Vivitrol relative to other for treatments of opioid use disorder:

- There are currently no specific clinical guidelines for transitioning patients with opioid use disorder to Vivitrol while minimizing the risk of precipitating withdrawal and relapse.[25] However, a number of opioid detoxification and induction strategies are being investigated to assist patients transitioning to Vivitrol.[90,91] The US prescribing recommendation that individuals abstain from opioids for seven to 10 days, combined with conventional methods of opioid-agonist tapering over several days, represents a delay of at least two weeks before Vivitrol can be started.[23,90] In addition, guidance is needed for transitioning patients from oral naltrexone, buprenorphine/naloxone, or methadone to Vivitrol or re-initiating treatment with Vivitrol following discontinuation.[23] Because of the time required for detoxification, current guidelines recommend residential or intensive outpatient settings for initiating treatment with Vivitrol.[2]
- Pain management is a concern in patients receiving treatment with Vivitrol.[25,92] Patients undergoing emergency or elective surgery will not respond to normal therapeutic doses of opioid analgesics because of the opioid-receptor antagonist mechanism of action of Vivitrol. In addition, re-initiating Vivitrol soon after opioid use may precipitate withdrawal. Therefore, it is recommended that pain be treated with regional or local anesthetic techniques, and non-opioid pharmacologic therapies (including ketorolac and gabapentin).[92] If non-opioid modalities prove ineffective or are contraindicated, the effects of opioid titration would need to be closely monitored by professionals trained in the management of the effects of high-dose opioids, including assisted ventilation and cardiopulmonary rescucitation.[92]
- There are currently no recommendations for the duration of treatment with Vivitrol.[25] An ongoing trial is assessing the effect of Vivitrol compared with placebo when given for 48 weeks versus 24 weeks in 130 patients addicted to opioids who have completed in-patient treatment.[93] Outcome measures include proportion with urine tests positive for opiates and HIV risk behaviours at 12 months.
- Following Vivitrol treatment, opioid tolerance is reduced from the pre-treatment baseline, and patients are vulnerable to potentially fatal overdose, particularly if they take large amounts of opioids in an attempt to overcome the blockade effect of Vivitrol.[23] None of the published phase III trials or studies in real-world settings have investigated the long-term risk of relapse, opioid overdose, and death among those participants who choose not to continue therapy with Vivitrol for longer than 78 months.
- Research comparing Vivitrol with oral naltrexone and with opioid agonists (such as methadone or buprenorphine/naloxone) is needed to improve our understanding of its place in therapy for opioid use disorder. One ongoing, randomized, open-label trial is assessing the comparative effectiveness of Vivitrol versus buprenorphine/naloxone in 600 adults with opioid use disorder in the US.[94] The primary outcome is time to opioid relapse (i.e., loss of persistent abstinence) during the 24-week treatment phase. Secondary outcomes include retention in treatment, opioid abstinence, HIV risk behaviours, quality of life, genetic moderators, and cost-effectiveness. A smaller randomized, open-label trial is also studying Vivitrol versus buprenorphine/naloxone in 180 patients with opioid use disorder in Norway.[95] Primary outcomes are abstinence from illicit opioids, as well as retention in treatment. Following the 12-week randomized period, there will be a 36-week period during which participants will continue to receive Vivitrol in order to investigate long-term outcomes. A third trial is investigating whether Vivitrol has greater efficacy and is more cost-effective than oral naltrexone, with or without behavioural therapy and HIV risk reduction counselling, in 320 opiate-dependent patients in Russia.[96] Primary outcome measures include reductions in HIV risk behaviours, reductions in illicit opiate use, and treatment retention during the six-month treatment phase and the six-month follow-up.
- There has been interest in using Vivitrol in various subpopulations, as agonist therapy with buprenorphine/naloxone or methadone may be less suitable for some patients. Several ongoing phase III and IV trials are evaluating the effect of Vivitrol in people within the criminal justice system, in those living with HIV, and in young adults and adolescents with opioid use disorder. Results from these and future studies will be needed to determine the clinical impact and value of Vivitrol in a broad and diverse population of patients with opioid use disorder.

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