Report to
The Vermont Legislature

Injectable Naltrexone: Feasibility, Effectiveness, Risks and Benefits

In Accordance with Act 169, 2014, ***An Act Relating to Operating a Motor Vehicle Under the Influence of Alcohol and Drugs,*** **Section 3.**

Submitted to: **House Committees on Human Services and on Judiciary**
Senate Committees on Health and Welfare and on Judiciary

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Executive Summary

In accordance with Act 169, The Vermont Department of Health Division of Alcohol and Drug Abuse Programs (VDH/ADAP) conducted a review of the "Feasibility, Effectiveness, Risks and Benefits of the Use of Injectable Naltrexone" for the treatment of opioid dependence. Naltrexone is an opioid antagonist medication that is approved by the Federal Drug Administration (FDA) for the treatment of both alcohol and opioid use disorders. In 2010 the FDA approved the 30 day injectable form of Naltrexone, called Vivitrol, for the prevention of relapse to opioids.

The research currently available suggests there may be benefits to those persons already detoxified from opioid drugs. Injectable Vivitrol offers the advantage of providing a consistent opioid receptor blockade to discourage opioid use for individuals at risk of opioid relapse. Vivitrol may be advantageous to some individuals with opioid use disorders as they exit controlled environments such as correctional facilities due to its requirement of a minimum of 7 days of opioid abstinence prior to initiation. However, because of the deficits in the current research there is a lack of convincing evidence to support the recommendation that Vivitrol is consistently effective.

Injectable Naltrexone: Feasibility, Effectiveness, Risks and Benefits

Act 169, 2014, Section 3
January 15, 2014

Introduction and Charge:

In response to the legislative charge contained within Act No.169, "The Department of Health shall evaluate the feasibility, effectiveness, risks, and benefits of using an injectable form of the opioid antagonist naltrexone in the treatment of opioid addiction in Vermont, either instead of or in addition to the use of methadone and buprenorphine." Naltrexone is an opiate receptor antagonist (blocker) that has been in use in an oral formulation since 1994 primarily for the treatment of alcohol dependence. Because of daily medication noncompliance issues, naltrexone has also been formulated in an extended release (monthly) injectable dose. Recently this formulation has been approved for use with opioid dependent individuals.

Methodology:

The Department conducted a thorough literature review and discussed current practices with clinical providers. In addition to reviewing available published research, the Vermont Department of Health, Division of Alcohol and Drug Abuse Programs (VDH/ADAP) program staff consulted with Suzanne Gelber, PhD. of the AVISA Group to further understand research protocols currently underway or those that have been concluded but have not yet undergone the peer review process.. Dr. Gelber has been a consultant to the federal Substance Abuse and Mental Health Services Administration (SAMHSA) and the Center for Substance Abuse Treatment (CSAT).

Overview:

According to a SAMHSA Advisory: The US Food and Drug Administration (FDA) approved extended release injectable naltrexone (Vivitrol) in October 2010 to treat people with opioid dependence. The injectable naltrexone, Vivitrol, provides patients with opioid dependence the

opportunity to take effective medication monthly, as opposed to the daily dosing required by other opioid dependence medications such as methadone, buprenorphine and oral naltrexone).[1]

The other advantage of extended release naltrexone is the potential to reduce treatment dropout due to the slow release of the drug over the 30 day time period.[2]

This offers the opportunity to engage a patient more consistently in psychosocial counseling in either individual or group settings. Research has clearly demonstrated that active and regular participation in psychosocial therapy in conjunction with medication assisted treatment (MAT) is more effective across a number of outcome domains than MAT alone. Oral naltrexone prescribed on a daily basis can only be effective if the dosing regimen (daily or at least several times per week) is routinely followed. If it is not routinely followed, clinical trials have shown that oral naltrexone is no more effective than placebo for opioid dependent patients

Feasibility:

Vivitrol is the only extended release injectable naltrexone product approved by the FDA as a treatment for opioid dependence. Currently the cost per dose is $1400[3]. At this time Vivitrol is not on hospital or pharmacy formularies. It needs to be ordered directly from the manufacturer to be sent to the physician's office for use and typically requires prior authorization from payers. In order to avoid serious withdrawal symptoms, patients need to be completely detoxified for a minimum of 7 days from opioids prior to any exposure to extended release Vivitrol . Currently, the standard of care for opioid dependence is a regimen of methadone or buprenorphine in conjunction with long-term psychosocial treatment, both of which have been shown to be efficacious and effective in the treatment of opioid use disorders.[4]

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[1] Substance Abuse and Mental Health Services Administration (2012). An Introduction to Extended-Release Injectable Naltrexone for the Treatment of People with Opioid Dependence. https://store.samhsa.gov/shin/content/SMA12-4682/SMA12-4682.pdf

[2] However, this is in a research context. It is possible that monthly Vivitrol injections could have the opposite effect whereby an individual thinks psychosocial is unnecessary. This is likely an educational issue to be resolved between physician and patient.

[3] Institute for Clinical and Economic Review (2014). Management of patients with opioid dependence: a review of clinical, delivery system, and policy options - Draft Report. The New England Comparative Effectiveness Public Advisory Council Public Meeting – June 20, 2014

[4] Volkow, N.D., Frieden, T. R., Hyde, P. S., & Cha, S. S. (2014). Medication-assisted therapies: tackling the opioid overdose epidemic. *New England Journal of Medicine, 370,* 2063-2066.

Effectiveness:

The FDA approval of Vivitrol was based on a single 6-month randomized clinical trial in Russia sponsored and funded by the developer of the drug (Alkermes) comparing monthly doses of the naltrexone to a placebo[5]. Results suggested that the Vivitrol group had greater proportion of weeks of confirmed abstinence, longer therapy retention rates, and lowered craving scores than did the placebo group.

However, only 53% of the Vivitrol group and 38% of the placebo group completed the full study; and despite the significant difference in the outcomes for the two groups there was a more positive response to the placebo than usual in placebo-controlled trials[6]. Russia was chosen as the research site because opioid agonist treatments are not available so a placebo trial was possible.

However, this has raised some concerns about a research protocol that did not compare the new treatment (Vivitrol) with the standard of care in the United States (methadone and/or buprenorphine) . This was acknowledged by the study authors ("…in countries with a viable system of opioid maintenance treatment, patient resistance to placebo treatment or ethical considerations might make it difficult to do a placebo-controlled trial" p.1512). This was further underscored in an accompanying editorial comment by Wolfe et al. (2011): "The FDA should justify why it has lowered the scientific, regulatory, and ethical standards in approving depot [extended release] naltrexone for treatment of opioid dependence."[7]

Risks: Wolfe et al (2011) have outlined risks associated with extended release naltrexone. Since Vivitrol has been on the market 19 deaths have been reported by the manufacturer (Alkermes). The FDA's Adverse Event Reporting System lists 51 deaths from extended release naltrexone between 2006-2010[8].

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[5] Krupitsky et al. (2011). Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicenter randomised trial. *Lancet, 377*, 1506-1513.

[6] Note another methodological problem with this study: determining group status in a placebo vs Vivitrol comparison is relatively simple. After being administered the drug an individual who uses an opiate will not feel the effects (or feel less of an effect than usual); an individual in the placebo group will.

[7] Wolfe et al. (2011). Concerns about injectable naltrexone for opioid dependence. *Lancet, 377*, 1468-1469.

[8] Since this period was before FDA approval of depot naltrexone for opioid dependence, these deaths are most likely from use of the drug for alcohol dependence.

The risk profile includes increased potential for opioid overdose toward the end of each dosing period, potential to attempt overcoming the blockade by using more than usual amounts of opioids, injection site pain and tissue necrosis, and possible adverse effects on liver function. Another concern is lack of follow-up monitoring and care after last dose of Vivitrol. This is especially concerning because this is an optimal time for a relapse and/or overdose to occur.

Benefits:

Once a month dosing removes the "missed dose" problem of daily oral administration and keeps the receptor blockade in place for an extended period.

The primary benefits are twofold: 1. Consistent opioid receptor blockade that discourages opioid use; 2. Potential for increased attendance at necessary psychosocial treatment episodes to resolve related and precipitating issues.

Simulated Model of 1000 Patients in New England in Various Treatment Modalities[9]*:*

The Institute for Clinical and Economic Review (ICER, 2014)) estimated outcomes and costs over the course of two years for 1000 simulated opioid dependent patients for several treatment options based on currently available prevalence and economic data from Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont see Table 1 below).
These simulated data suggest that methadone maintenance treatment and buprenorphine maintenance treatment are more cost effective and produce better and safer outcomes than either formulation of naltrexone (oral or Vivitrol). This is consistent with previous research that has demonstrated significantly better outcomes for maintenance therapies than a detoxification approach (both including psychosocial adjunctive treatment) for both adolescents and adults.[10]

[9] Adapted from Institute for Clinical and Economic Review (2014) – Table ES3. Management of patients with opioid dependence: a review of clinical, delivery system, and policy options – Draft Report. The New England Comparative Effectiveness Public Advisory Council Public Meeting – June 20, 2014.

[10] Mattick RP, Breen C, Kimber J, Davoli M . (2014). Buprenorphine maintenance or placebo or methadone maintenance for opioid dependence. Cochrane Database Systematic Review, Feb 6;2:CD002207.
Weiss, et al. (2011). Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase, randomized controlled trial. *Archives of General Psychiatry, 68*, 1238-1246.
Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *Cochrane Database Syst Rev*. 2011a;9:CD005031.

Table 1: Simulated 2-Year Outcomes and Costs of 1000 Opioid Dependent Patients in New England

Outcome/Cost	**Methadone**	**Buprenorphine**	**Vivitrol**	**Oral Naltrexone**
Per 1000 Patients				
In treatment	630	523	416	277
Relapsed	185	292	400	538
Drug –free	177	176	173	169
Died	8	9	12	16
Costs - $/Patient				
Drug therapy	699	3,655	6,585	665
Other SA services	14,017	7,043	2,985	2,446
Other health care	23,926	25,993	28,109	30,844
SUBTOTAL	***38,642***	***36,691***	***37,679***	***33,954***
Social costs	92,068	102,337	119,239	141,076
TOTAL	***130,710***	***139,028***	***156,918***	***175,030***

ICER estimates that the two-year social cost of not initiating any treatment is $200,000[11].

Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. *Cochrane Database Syst Rev*. 2011b;10:CD004147

Minozzi S, Amato L, Davoli M. Detoxification treatments for opiate dependent adolescents. *Cochrane Database Syst Rev*. 2009a;4:CD006749

Minozzi S, Amato L, Davoli M. Maintenance treatments for opiate dependent adolescents. *Cochrane Database Syst Rev*. 2009b;2:CD007210.

Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev*. 2011;4:CD001333.

[11] Social costs include law enforcement, victimization, and lost productivity.

Previous research on Vivitrol for Alcohol Dependence:

Vivitrol was approved by the FDA for treating alcohol dependence in April, 2006. Approval was primarily based on a multi-center, randomized, placebo-controlled study comparing two dosages of injectable naltrexone (380mg and 190mg) to placebo injections administered monthly over a 6 month period[12]. This study is notable for several reasons. First, the primary outcome measure was the number of heavy drinking days; the higher dose of naltrexone demonstrated a modestly significant reduction while the lower dose did not.

The authors stated: "Patients in all 3 treatment groups [including placebo] substantially reduced the number of heavy drinking days compared with their pretreatment levels." However, no reductions were observed in female participants in either the 380mg or 190mg group. Second, while the study did not require an abstinence period lead-in, 9% of the study population was abstinent in the seven days prior to treatment. In both the high and low dose naltrexone groups, lead-in abstinence was associated with significantly better outcomes. Third, over the six month period, complete abstinence was maintained by 7% of the 380mg group, 6% of the 190mg group, and 5% of the placebo group[13].

Three additional studies have been published from this same data set.

The first investigated "holiday drinking" in a small number of patients who maintained abstinence at least 4 days prior to study initiation [14]. These groups were compared on percent drinking days, percent heavy drinking days, and the number of drinks per day for both holiday and non-holiday periods[15]. The authors found that patients in both naltrexone groups were

[12] Garbutt et al. (2005). Efficacy and tolerability of long-acting injectable naltresone for alcohol dependence: A randomized clinical trial. *Journal of the American Medical Association, 293*, 1617-1625.

[13] This study and most other studies concerning Vivitrol were sponsored by Alkermes, the manufacturer of Vivatrol. All the authors (8) list financial ties to Alkermes. In addition, the "Role of the sponsor" is presented as: "Data were collected and monitored by Alkermes and Pharmaceutical Product Development, Inc., a contract research organization. Data were managed and analyzed by Alkermes clinical and regulatory personnel and were interpreted by authors on the study with input from Alkermes clinical and statistical staff."

[14] Lapham et al. (2009). The effects of extended-release naltrexone on holiday drinking in alcohol-dependent patients. Journal of Substance Abuse Treatment, 36, 1-6. Sample size: $n_{380mg} = 28$; $n_{190mg} = 26$; $n_{placebo} = 28$

[15] Holidays: New Year's, Labor Day, Fourth of July, Super Bowl Sunday, Christmas, Memoorial Day, Thanksgiving, Halloween, and St. Patrick's Day.

significantly lower on all three variables of interest compared to the placebo group for both holidays and non-holidays[16].

The second study[17] was very similar to the original but looked at only those patients who reported a lead-in abstinence period and provided substantially similar results. The 380mg group had significantly higher rates of initial abstinence, fewer drinking days, fewer heavy drinking days, and longer time to first episode of heavy drinking compared to the placebo group. The 190mg group had results that were intermediate between the 380mg and placebo groups.

The third study based on the original 2006 data investigated the effectiveness of Vivitrol in more severely dependent patients[18]. This study omitted the 190mg dose because the 380mg dose is currently the clinically approved and available dose[19]. Reduction in heavy drinking days (380mg group = 37.3%; placebo group = 27.4%) was significant among patients who were assessed as more severely alcohol dependent. None of these studies subsequent to the 2006 original report investigated differential gender effects - likely due to small sample sizes.

Another study tested the efficacy of extended release naltrexone with volunteers from a criminal justice population (either DUI or another offense with co-occurring alcohol disorder)[20]. Subjects in the control group were matched post-hoc on five demographic variables[21]. Participants in the Vivitrol group were to receive monthly injections for at least 9 months, although, because of a lack of compliance, the average number of injections over the 9 months was 4.3.

[16] Two of the five authors (Dr. Lapham and Bohn) received research support from Alkermes. The other three Dr.s Forman, Alexander, and Illepeuruma) are employed by Alkermes. "The study analysis and writing support were sponsored by Alkermes, Inc., Cambridge, MA, amd Cephalob, Inc., Frazer, MA." (p.5)

[17] O'Malley et al. (2007). Efficacy of extended-release naltrexone in alcohol dependent patients who are abstinent before treatment. *Journal of Clinical Psychpharmacology, 27*, 507-512.

[18] Pettinati et al. (2011). Efficacy of extended-release naltrexone in patients with relatively higher severity of alcohol dependence. *Alcoholism: Clinical and Experimental Research, 35*, 1804-1811.

[19] While this is a viable approach it would have been interesting to see any results from the 190mg group given that the other studies have suggested that this group has intermediate outcomes (e.g., the "holiday drinking" study mentioned above as well as the original study).

[20] Finigan et al. (2011). Preliminary evaluation of extended-release naltrexone in Michigan and Missouri drug courts. *Journal of Substance Abuse Treatment, 41*, 288-293.

[21] This was a retrospective study so no placebo control group was available.

Both groups also received standard care through drug courts[22]. Of the four outcomes presented, three showed no difference between the Vivitrol group and the demographically matched controls[23].

Research Conclusions:

Monthly injectable naltrexone in conjunction with psychosocial treatment appears to be efficacious for alcohol dependent males who have discontinued alcohol consumption for at least 4 days prior to initial treatment. As mentioned earlier, the main benefit of Vivitrol appears to accrue to patients who won't or can't follow a daily dosing regimen of oral naltrexone. It is important to note that no study reported the effects of Vivitrol in isolation; that is, injectable naltrexone is used in combination with psychosocial treatment. The limited data on Vivitrol for opioid addicted individuals suggest that it may be a viable alternative for special populations such as individuals from the criminal justice system or individuals who have difficulty with a daily medicine regimen. Finally, we note again the data showing the ineffectiveness of Vivitrol for women with an alcohol disorder. Gender data from the original Vivitrol study for opioid abuse was not included in the published analyses likely because there were so few who participated in the study (13 in the Vivitrol group and 17 in the placebo group). In any case this remains an open but important question.

Conclusions and Recommendations

1. Injectable naltrexone (Vivitrol) received FDA approval for the prevention of relapse to opioids in October 2010. To date, research findings demonstrate its effectiveness in narrowly defined groups of individuals diagnosed with opiate dependence. We note these conclusions are based on a relatively limited research base, but that more research is currently underway and additional peer reviewed publications are forthcoming.
2. The 30-day injectable formulation suggests some possible utility for individuals no longer physiologically dependent upon opioids, but at high risk of relapse such as

[22] Standard Care consisted of group treatment, individual treatment, drug court sessions, 12-step self-help meetings. In addition, all participants provided at least 4 random breath alcohol or urine tests per week for the first month, two per week for the next 3 months, and one per week subsequently.

[23] Three of the five authors were "paid consultants for Alkermes, Inc. in connection to this study. Dr. Edward Schweizer of Paladin Consulting Group, a paid consultant to Alkermes, Inc., provided editorial assistance on an early draft of this article." Other disclosures: "This study was funded by Alkermes, Inc., under a contract with NPC Research. Research design, data collection, data analysis, and report writing were performed primarily by NPC Research."

individuals exiting the criminal justice system, those for whom daily medication adherence is a concern, or for those who decline agonist/partial agonist therapy. Given the requirement for individuals to be a minimum of 7 days abstinent from opioids prior to the initial dose, injectable naltrexone does not appear to be a substitute for buprenorphine or methadone for active opioid users.

3. Given the relatively new FDA approval of the medication for the prevention of relapse to opioids, the continued monitoring and evaluation of peer-reviewed research findings is warranted. Research with diverse demographic groups (e.g., age, gender, ethnicity, etc.) can assist in ascertaining potential populations for whom the medication may be clinically indicated or contraindicated.

4. Due to its antagonist effects, it is important to note that individuals requiring opioid pain relievers are not viable candidates for this medication because injectable naltrexone would also block the analgesic effects from opioid based pain medications.

Thus, injectable naltrexone may have limited utility in treating addicted but detoxified individuals who do not have access to or do not desire the current standard of care which is the use of methadone or buprenorphine