CODA inc.
health - recovery - community

Thank you for the opportunity to share my perspective supporting enhanced patient access to extended-release naltrexone (Vivitrol®). I am the Director of Research at CODA, Inc., a non-profit substance abuse treatment center providing treatment for over 1000 opioid dependent patients a year in Portland. CODA was an early adopter of Vivitrol® beginning in 2011 with a National Institute on Drug Abuse (NIDA) study. As an epidemiologist, I see clearly the burgeoning opioid dependence problem and the ongoing alcohol dependence problem within our community.

The Substance Abuse and Mental Health Services Administration (SAMHSA) lists Vivitrol® as one of the three first-line medication treatment options for opioid dependence, along with buprenorphine and methadone. In fact, SAMHSA stresses some of the advantages of Vivitrol® – it delivers extended treatment for approximately 30 days, something neither methadone nor buprenorphine can provide. This type of medication adherence is essential as the risk of relapse to using illicit opioids without medication support is 99%. As a non-opioid it does not cause dependence and fills a void previously unavailable - simultaneously treating both opioid and alcohol dependence. Alcohol dependence is a common poly-substance co-dependence occurring in approximately 30% to 40% of opioid dependent patients. Because it is not a controlled medication, Vivitrol® can be prescribed by physicians, nurse practitioners and physician assistants without additional restrictions or licensing requirements. Thus, Vivitrol® is more accessible than either methadone or buprenorphine due to prescriber restrictions. Constraining Vivitrol® and removing it from the first-line of opioid treatment - by first requiring methadone and buprenorphine failure - will have particularly deleterious treatment effects in more rural communities where methadone and buprenorphine prescribers are rare or non-existent.

Given that Vivitrol® is an opioid blocker, a non-opioid, and does not create dependence, it has received much wider acceptance within and from the criminal justice system than either methadone or buprenorphine ever has. *Why is this relationship with the criminal justice system key?* A history of incarceration is common among opioid dependent individuals, 78% of CODA's opioid treatment population report ever being incarcerated. CODA, in partnership with Multnomah County, is having great success with providing Vivitrol® to individuals recently released from incarceration. *Why is this critical?* For individuals exiting jails or prisons, the risk of death from overdose within two weeks of release is 129 times that of other causes of death and 95% of these deaths are attributable to opioids. Neither buprenorphine nor methadone would reach therapeutic levels in time to prevent this, assuming the unlikely possibility of these individuals entering treatment immediately after release.

Adding additional barriers to Vivitrol® treatment access are discriminatory to those in rural areas; will decrease treatment options available to those involved in the criminal justice system; will likely decrease early adherence to medication; and therefore creates an unnecessary barrier to treatment. Those of us who work with these patients on a daily basis value the strengths of having Vivitrol® available as a first-line treatment medication. I am a co-author of a meta-analysis reviewing medical care utilization among patients on medication for alcohol and opioid use disorders. The data are clear – patients on medication have reduced health care utilization and expense. Generally, patients on extended-release naltrexone have greater reductions in health care utilization and therefore, reduced health-care expenses. Please see attached paper (under review). I firmly believe that continuing first-line access to Vivitrol® will not only provide another much needed treatment for opioid and alcohol dependence, but will also decrease morbidity, mortality, and improve the quality of life of patients who suffer from addiction.

Sincerely,

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Health Economic Meta-Analysis of Alcohol and Opioid Dependence Treatments

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Abstract

Objective: Medication adherence is an important determinant of success in the treatment of substance use disorders. With FDA-approval of once-monthly injectable extended-release naltrexone (XR-NTX), there is a need for health economic analysis of approved agents for alcohol and opioid dependence treatment. The objective of this study was to evaluate cost and utilization outcomes between XR-NTX and other pharmacotherapies for treatment of alcohol and opioid dependence.

Methods: Published studies were identified through comprehensive search of two electronic databases. Studies were included if they compared XR-NTX to other approved medicines and reported economic and healthcare utilization outcomes in patients with opioid or alcohol dependence. Reported outcomes were synthesized using random-effects meta-analyses.

Results: We identified five observational studies comparing 1,565 patients using XR-NTX to other therapies for alcohol and opioid dependence. Alcohol dependent XR-NTX patients had longer medication refill persistence versus acamprosate and oral naltrexone. Healthcare utilization was generally lower and costs were as low or lower in XR-NTX-treated patients versus other alcohol dependence agents. XR-NTX patients had $2729 lower total cost over 6 months versus acamprosate (95% CI -$4482 – -$976). Opioid dependent XR-NTX patients had lower inpatient substance abuse-related utilization versus other agents and $8170 lower total cost versus methadone (95% CI -$12286 – -$4054), although this single study had a small sample size.

Conclusions: XR-NTX patients experienced less frequent substance-related hospitalization, with six-month health care costs that are no greater relative to other approved medications for alcohol dependence. Findings were similar with opioid dependence, although more research is needed.

Introduction

Alcohol and drug use disorders affect over 21 million Americans (8% of the US population)[1] and complicate the hospital and primary care management of chronic conditions as far-ranging as diabetes, depression and osteoporotic bone fracture, arthritis, headache and lower back pain. [2-4] In New York State, hospitalized patients with substance abuse had a preventable hospital readmission rate of 10.3 admissions per patient per year versus 4.8 among patients without behavioral conditions.[5] Studies consistently demonstrate appropriate treatment of substance abuse can reduce hospitalizations and emergency department (ED) utilization.[6,7] Despite this, alcohol dependence treatment ranks lowest in evidence-based practice among 25 health and behavioral health conditions.[8]

The US government recommends pharmacotherapy as a standard of care in alcohol and opioid dependence[9,10] and the Food and Drug Administration (FDA) has approved four medications for treatment of alcohol dependence (i.e., acamprosate, disulfiram, oral naltrexone [NTX-PO] and extended-release naltrexone [XR-NTX]) and four medications for treatment of opioid dependence (i.e., two μ-opioid agonists or substitution agents: buprenorphine alone and in combination with the opioid antagonist naloxone and methadone; and two opioid antagonists, NTX-PO and XR-NTX).

Medication-assisted therapy, however, is under-utilized. Within a nationally representative sample of 345 privately-funded addiction treatment centers, only 24% used pharmacotherapy for alcohol dependence and 34% reported use of pharmacotherapy for opioid dependence.[11] Similarly, among 154 programs in the National Institute on Drug Abuse Treatment Clinical Trials Network (CTN), less than 20% used an alcohol dependence agent and only 10% of patients with opioid dependence received agonist or antagonist medication.[12] Barriers to the use of medication include financing, medical staffing, logistical support, education and attitudes.[13]

As in other chronic conditions[14,15], medication adherence in substance abuse disorders is a major challenge to effective treatment.[16,17] In one study, less than half of alcohol dependent patients filled more than

their initial NTX-PO prescription and only 14% were adherent over a 6 month period.[18] All currently approved agents are oral formulations intended for daily self-administration, except once-monthly, injectable XR-NTX.[19]

The Institute of Medicine identified substance use disorders as a high priority need for comparative effectiveness reviews (CERs)[20] and CERs need to be regularly updated to optimize health care and policy decisions.[21] The emergence of pharmacotherapies for treatment of alcohol and drug use disorders has led to the publication of several observational studies that constitute comparative effectiveness research. To examine comparative effectiveness in alcohol and opioid dependence treatments, we conducted a meta-analysis of existing studies to determine the cost and utilization impact of non-medicated treatment, medication-assisted treatment, and in particular among the latter group, the most recently approved agent, XR-NTX, in patients with these disorders.

Methods

We searched MEDLINE and CINAHL (latest update on October 19, 2012) for observational and interventional studies using the following keyword search strategy: "naltrexone" or "Vivitrol" or "extended-release naltrexone" AND "healthcare utilization" or "utilization" or "costs." Eligible studies evaluated one or more of these outcomes: medication adherence, service utilization (detoxification, inpatient, outpatient, ED), and healthcare expenditures in populations being treated for alcohol or opioid dependence disorders. Studies were excluded if they did not specifically compare XR-NTX to one or more substance abuse medications for one or more of the outcomes described above.

We extracted the results into an evidence table including author, population studied, year of publication, treatments evaluated, inclusion and exclusion criteria, number of subjects screened and enrolled, age, sex, disease severity, analytic method, confounder adjustment, outpatient utilization, inpatient utilization, medication adherence, inpatient costs and study quality. We rated study quality on three domains using the Newcastle-Ottawa Scale (NOS) quality assessment tool.[22] The NOS is a rating scale to evaluate the quality of observational research – higher scores reflect better quality. Studies receive up to 9 points distributed among 3 domains: exposure selection (4 points), comparability of comparison groups (2 points) and outcome assessments (3 points).

Outcomes were predominately continuous and differences between treatment regimens were explored using random-effects meta-analysis. For similar but non-identical outcome variables, we pooled the standardized mean difference (SMD) using Hedge's *g* to estimate effect sizes (0.2 represents a small effect, 0.5 is a moderate effect, and 0.8 is a large effect).[23] We calculated unreported standard deviations based on reported p-values or 95% confidence intervals using established methods.[24] Statistical heterogeneity was explored both qualitatively, through comparison of study population settings, treatments, and methodology, and quantitatively using the I^2 statistic and selected sensitivity analyses.[25] The I^2 statistic is used in meta-analyses to quantify the degree of variation among studies caused by heterogeneity over statistically chance. If significant heterogeneity

was present, we qualitatively assessed the component studies and excluded specific studies to evaluate the impact on results. We did not conduct formal analyses for publication bias because of the small number of studies identified.[26] All statistical analyses were conducted using Stata/IC 11.0 (StataCorp LP, College Station TX).

Results

Figure 1 summarizes the study search and study selection results. The keyword literature search found 111 study citations. After screening abstracts, we retrieved full text for 11 studies deemed to be germane to our synthesis. No interventional studies and five observational studies met inclusion criteria.[27-31] Table 1 in the online supplement summarizes key study characteristics and study results. Four studies were retrospective cohort studies using administrative claims data from commercial health plans.[28-31] Three studies (two in alcohol dependence and one in opioid dependence) compared patients receiving any pharmacotherapy to unmedicated patients.[28-30] Four studies compared the impact of XR-NTX versus other agents, using differing analytic approaches with a variety of healthcare and medication utilization outcomes over 6 months. A fifth study, based on administrative data from the Veterans Health Administration (VHA), assessed adherence in patients using XR-NTX, NTX-PO, acamprosate or disulfiram for alcohol abuse.[27] Four studies examined alcohol dependence[27,28,30,31], and one examined opioid dependence.[29]

Studies represented a mixture of both manufacturer-sponsored[28-30] and independent research.[27,31] The Newcastle-Ottawa Scale scores were comparable across the five studies and ranged from 7 to 8 out of 9 total points. All but one study used a variety of statistical approaches to control for confounding and baseline imbalance: two studies of alcohol dependent patients used propensity score[28,30] and the opioid dependence study used instrumental variable analysis.[29] Covariates considered for adjustment were generally comprehensive and included key demographics, psychiatric diagnoses, comorbidity scores (e.g. Deyo-Charlson) and baseline healthcare utilization. One analysis used difference-in-differences analysis with adjustment for demographic variables but not comorbidities.[31] The VA study did not statistically adjust measures of adherence using baseline comorbidity variables.[27]

Medication Refill Persistence

The remaining meta-analyses explore outcomes within the medication groups. Five studies examined medication adherence and reported the proportion of days covered (PDC) or a similar value measuring the ratio of days' supply dispensed to total days in the observation period (180 days).[27-31] For one study, we were able to obtain total days' supply dispensed for each drug from a co-author.[31] Figure 2 shows the pooled differences in the numbers of days covered by medication for XR-NTX versus comparators, by study population. Among the alcohol dependence studies, XR-NTX was consistently associated with longer medication persistence compared to oral agents, from 9.4 days longer (95% CI 4.3 – 14.5) versus NTX-PO to 15.9 days (95% CI 10.0 –21.8) versus acamprosate. Compared to disulfiram, the greater mean duration with XR-NTX did not reach significance, however heterogeneity was quite high. In opioid dependence, XR-NTX was not associated with significant differences in medication days covered relative to any comparator.

Detoxification Facility Use

Three studies analyzed inpatient detoxification facility utilization during the six months following the initial treatment.[28-30] In alcohol dependence, Figure 3 suggests that XR-NTX was associated with significant reductions of 201 fewer days/1000 patients (95% CI -6 – -396) in detoxification facilities versus disulfiram and 487 fewer days/1000 patients (95% CI -161 – -814) versus acamprosate. With opioid dependence agents, however, differences in days of detoxification were not significant.

Substance-abuse Related Inpatient Utilization

Four studies reported inpatient utilization for alcohol or opioid dependence[28-31] but one analysis did not differentiate substance-related (e.g., for alcoholic pancreatitis or infectious cellulitis) versus unrelated inpatient utilization (e.g., possibly substance related but not coded as such)[31] and one reported only inpatient days while the others reported admissions.[28] To manage these differences, we pooled the SMD in inpatient utilization (admission or inpatient days) across studies. As shown in Figure 4, XR-NTX was associated with significantly less inpatient substance-related utilization relative to all medications across both alcohol and opioid dependence

studies. The decrease in inpatient utilization was fairly consistent in both populations. In alcohol dependence, inpatient utilization reductions with XR-NTX ranged in SMD from -0.10 (95% CI -0.20 – 0.00) versus NTX-PO to -0.12 (95% CI -0.20 – -0.04) versus disulfiram. In opioid dependence, the reduction with XR-NTX in SMD ranged from -0.19 (95% CI -0.35 – -0.02) versus methadone to -0.24 (95% CI -0.42 – -0.07) versus NTX-PO. Excluding the Bryson analysis (29) did not change the point estimates appreciably, however, all three comparisons became non-significant: NTX-PO (pooled SMD -0.10; 95% CI -0.25 – 0.06), disulfiram (pooled SMD -0.11; 95% CI -0.23 – 0.02), acamprosate (pooled SMD -0.11; 95% CI -0.22 – 0.001).

Emergency Department Utilization

Four studies reported ED visits.[28-31] Because Mark et al.[28] only reported alcohol-related ED utilization, we calculated the SMD for each study. In studies of alcohol dependent patients we found no significant differences in ED utilization for XR-NTX versus other agents. In the opioid study, XR-NTX was associated with a 982 visit reduction/1000 patients ($p < 0.0001$) versus methadone, corresponding to a 0.32 reduction in SMD (95% CI -0.08 – -0.01).

Total Costs

Two papers reported the total of all inpatient, outpatient, addiction specialty, medical and pharmaceutical costs during the six months post index treatment[29,30] and a third examined total costs excluding pharmacy.[31] Figure 5 shows the forest plot for a meta-analysis on total cost. In no comparison was XR-NTX associated with significantly greater overall healthcare costs. In the two alcohol dependence studies, XR-NTX patients had lower total cost versus acamprosate (-$2729; 95% CI -$4482 – -$976). Excluding the Bryson et al. data (29) did not substantially alter the result (-$3588; 95% CI -$5396 – -$1780). In opioid dependence, XR-NTX patients had significantly lower total costs versus methadone (-$8170; 95% CI -12286 – -4054).

Conversion to Clinical Metrics

Table 2 in the online supplement summarizes pooled estimates from these studies along with a transformation into more clinically meaningful metrics. The cost and utilization estimates were rescaled to

reflect the number of patients required to be treated with XR-NTX over the alternative medication in order to achieve a particular reduction. We converted the inpatient substance abuse-related SMD to days/per 1000 patients by multiplying the pooled estimate by the pooled standard deviation (5935), which was calculated from data provided by Mark and colleagues for XR-NTX.[28] These data suggest that a 30 day reduction in detoxification facility utilization can be achieved by treating between 62 and 149 patients with XR-NTX instead of acamprosate or disulfiram respectively. Similarly, we estimate that treating as few as 14 patients with XR-NTX instead of acamprosate or 68 patients instead of NTX-PO will avoid $10,000 in spending for substance abuse-related inpatient care. Only 4 additional patients would need to be treated with XR-NTX over acamprosate to achieve a reduction in $10,000 in total costs during a six month observation period.

Medication versus No Medication

Three of the studies pooled patients taking any medication and compared them with patients who received treatment for a substance dependence diagnosis but without an approved pharmaceutical.[28-30] Bryson and colleagues[31] compared patients receiving XR-NTX to those who received psychosocial treatment, in particular, and the study was included in sensitivity analyses. Across three studies, treatment with any medication was associated with 2594 fewer days (per 1000 patients) of detoxification facility use (95% CI 580 – 4609, I^2=100%) over a six month period. Heterogeneity was very high, as estimates varied widely from study to study. In alcohol dependence, medication was associated with significant reductions in detoxification facility use (per 1000 patients) that ranged from 457 fewer days (95% CI 252 – 662) to 3014 fewer days (95% CI 2866 – 3162) versus non-medicated care. In opioid dependence,[29] medication was associated with 4311 fewer days (95% CI 4115 – 4507) in detoxification facility use (per 1000 patients). We used SMD to combine inpatient substance abuse admissions or days among the three reporting studies.[28-30] Medication was associated with a SMD reduction of 0.54 (95% CI 0.16 – 0.91, I^2=100%) but again heterogeneity across studies was very high. Sensitivity analysis including the Bryson study[31] did not change results appreciably. Among the alcohol dependence studies, the individual SMD effect sizes ranged from -0.10 (95% CI -0.15 – -0.05) to -0.63 (95% CI -0.66 – -0.60). In opioid dependence, medication was associated with an effect size of -0.88 (95% CI -0.92 – -

0.85).[29] Three studies reported total costs for any medication versus none (27;28;31) and the Bryson study[31] reported total non-pharmacy costs for XR-NTX versus no medication. Overall, total costs were lower by an average of $3649 (95% CI $3181 – $4117; I^2=18%) in patients receiving a medication versus those who did not. Removing the Bryson data did not substantially affect this estimate.

Discussion

The meta-analysis suggests among the approved pharmacotherapies, alcohol dependent XR-NTX patients had as low or lower healthcare costs, with the longest medication persistence and the least inpatient utilization. Although prior work described the efficacy of oral agents as inconsistent and modest, our analyses, in contrast, show relatively consistent cost and utilization reductions associated with use of XR-NTX.[32] Although not the primary aim of this study, we found that alcohol or opioid dependent patients who do not receive an approved pharmacotherapy experience higher six-month healthcare costs and more hospitalization.

In opioid dependence, XR-NTX patients also had similar or lower costs and less substance-related inpatient utilization than patients treated with other agents. Statistical power, however, may have been limited given the availability of only a single opioid dependence study and a relatively smaller number of patients treated with XR-NTX (n=156). The generally positive XR-NTX effects for opioid dependence may be unexpected because the standard of care has been agonist medications. Many patients reluctant to initiate agonist therapy, however, may find a long-acting opioid antagonist useful in the course of recovery. Additional utilization analyses in opioid dependence are required to fully assess the relative advantages and disadvantages of agonist and antagonist therapy, and the optimal duration of treatment. Benefit from opioid substitution treatment is expected when treatment extends beyond one year,[33] however, the Baser study of opioid dependence agents found a substantially shorter mean duration.[29] Meanwhile, the optimal duration with extended antagonist therapy has not been specified and remains an individualized clinical decision.

Limitations and Strengths

Limitations of these studies include the use of slightly different outcome measures, although we used a SMD approach to accommodate the variation. Patients were not randomly assigned, leaving the potential for residual confounding,[34] although these studies employed rigorous controls for pre-treatment patient variation. Comparisons between medication treatment and no medication treatment could be particularly problematic

because of significant unmeasured differences in severity of illness. With observational designs, pooled estimates may still have issues related to internal, and perhaps external, validity of the original research. Generalizability could be an issue as four of five studies, reflect commercially insured patients only, and were limited to six month study periods. Research from publically funded healthcare programs would be helpful for establishing the comparative benefits of XR-NTX for those of lower socio-economic status who are disproportionally affected by substance abuse disorders. In light of the approaching coverage expansion as part of the Affordable Care Act, similar studies conducted within state Medicaid programs are needed. The small number of eligible studies reflects the relatively recent approval of XR-NTX for alcohol and opioid use disorders. The opioid dependence data require replication because they are based on one study with data collected prior to FDA approval of XR-NTX for opioid dependence treatment. Although we summarize the aggregate medication versus no-medication comparisons presented in three of the studies, these results must be viewed as exploratory because the primary goal and search was for studies examining treatment with XR-NTX. Treatment effect for medication versus no medication comparisons appear to be quite large, especially when compared to individual drug effects, however heterogeneity between the studies was high and pooled estimates may not be reliable. Finally, because we only found five relevant studies, our findings could be altered by any unpublished negative studies.

Despite these limitations, comparative research using retrospective database analysis provides effectiveness data, addresses broader populations than efficacy trials, and has increased policy relevance.[20] Our analysis used real-world data from naturalistic community treatment, and included nearly 50,000 patients receiving medication and 1,565 receiving XR-NTX, making it the only comprehensive analysis across all approved substance-dependence pharmacotherapies, to date. The analyses using multiple data sets found generally consistent results across a diversity of payers despite variability in benefits covered, patient populations and case-mix control methods.

We encourage continued analyses of healthcare utilization data. States have begun to build All-Payer All-Claims data bases and such data could provide comprehensive analyses across commercial and public

health plans. Subsequent analyses should include public insurance data, track longer durations of treatment and post-treatment, and elucidate patient characteristics and treatment patterns that predict optimal health economic outcomes and patient benefit. Also, the evidence base could benefit from a larger study of XR-NTX in opioid dependence.

Finally, given the lack of meaningful adoption of pharmacotherapy in addiction treatment, general medicine physicians, hospitals, insurers and policymakers need to explore innovative means of fostering such growth, including disease management and integration with general medical care. Alcohol and drug treatment services remain ambivalent, at best, toward the use of medication despite: a) clinical trials documenting the efficacy of pharmacotherapy;[35-37] b) the availability of FDA-approved medications; and c) national consensus standards recommending pharmacotherapy.[38] Both alcohol and opioid dependence can be successfully addressed in primary care settings[39] and physicians have used XR-NTX successfully in both hospital and community-based general internal medicine practices.[40] The reductions in costs and utilization found in the present study with medication, and in particular with XR-NTX, may be relevant for accountable care organizations or patient-centered medical home models. Given rising pressures to reduce potentially preventable hospital readmissions and other reducible cost and morbidity causes, the optimization of patient care and management of resources warrant systemic change in the delivery of addiction treatment in the advancing era of health care reform.

Table and Figure Legends

Figure 1: CONSORT flow diagram of studies reviewed. Excluded comparison studies did not compare XR-NTX to other treatments. Excluded outcome studies did not examine relevant outcomes.

Figure 2: Meta-analysis of XR-NTX compared to other pharmaceutical treatments for alcohol or opioid dependence on adherence as measured by days of medication coverage over 180 days. NTX-PO = oral naltrexone. XR-NTX = extended-release naltrexone.

Figure 3: Meta-analysis of XR-NTX compared to other pharmaceutical treatments for alcohol or opioid dependence on detoxification facility days (per 1000 patients). NTX-PO = oral naltrexone. XR-NTX = extended-release naltrexone.

Figure 4: Meta-analysis of XR-NTX compared to other pharmaceutical treatments for alcohol or opioid dependence on standard mean difference (SMD) of substance-abuse related inpatient days or admissions. *Bryson study only reports total inpatient days. NTX-PO = oral naltrexone. XR-NTX = extended-release naltrexone.

Figure 5: Meta-analysis of XR-NTX compared to other pharmaceutical treatments for alcohol or opioid dependence on total costs. *Bryson study only reports total non-pharmacy costs. NTX-PO = oral naltrexone. XR-NTX = extended-release naltrexone.

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Katie Bensching, M.D.
Interim Division Chief

Oregon Pharmacy & Therapeutics Committee

Re: Vivitrol on the Preferred Drug List

October 17, 2013

Dear Oregon Pharmacy & Therapeutics Committee Members,

Thank you for the opportunity to share my experiences with Vivitrol. I am both the medical director of CODA, Inc, a non-profit substance abuse treatment center providing medication treatment for over 1000 opioid dependent patients a year in Portland, and an Assistant Professor of Medicine at Oregon Health and Science University in the Internal Medicine department. I am Board Certified in both Internal Medicine and Addiction Medicine. I see clearly the burgeoning opioid dependence problem and the ongoing alcohol dependence problem within our community from both an academic and treatment level perspective. Vivitrol fills a void previously unavailable for combating the opioid epidemic and treating alcohol dependence.

The Substance Abuse and Mental Health Services Administration (SAMHSA) lists Vivitrol as one of the three first-line medication treatment options for opioid dependence, along with buprenorphine and methadone. In fact, SAMHSA stresses some of the advantages of Vivitrol – it provides extended treatment for up to 30 days, thus ensuring medication adherence – neither methadone nor buprenorphine can provide this. As a non-opioid it also does not cause dependence, it is the only medication that provides cross treatment for alcohol (a common poly-substance dependence of approximately 30% to 40% in opioid dependent patients), and because it is not a Schedule II or III medication it can be prescribed by physicians, NPs and PAs without additional restrictions or licensing requirements.

Given that Vivitrol is an opioid blocker and non-opioid, it has received much wider acceptance within and from the criminal justice system than either methadone or buprenorphine ever has. Why is this relationship with the criminal justice system key? Seventy-eight percent of opioid dependent patients at CODA have a history of incarceration. CODA, in partnership with Multnomah County, is having great success with providing Vivitrol to individuals recently released from incarceration. Why is this critical? For individuals released from jails or prisons, the risk of death from overdose is 129.0 times that of other causes of death and 95% of these deaths are attributable to opioids. Neither buprenorphine nor methadone would reach therapeutic levels in time to prevent this, assuming it were possible to get patients into treatment immediately after release.

I firmly believe that increased access to Vivitrol will not only provide another much needed treatment for opioid and alcohol dependence, but will also decrease morbidity, mortality, and improve the quality of life of patients who suffer from addiction. I think that additional barriers to treatment (i.e. requiring prior authorizations before treatment) are an unnecessary and potentially dangerous barrier. Those of us who treat these patients on a daily basis would greatly value having another medication in our armamentarium.

I would be happy to comment further about this medication and my experience with it if you have any questions.

Sincerely,

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weimerm@ohsu.edu

October 17, 2013

Oregon Pharmacy and Therapeutics Committee
Clackamas Community Training Center
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Wilsonville, OR 97070

To the Committee:

The discussion of Vivitrol's® place on the Preferred Drug List is timely and of great interest to those of us working in the field of addictions treatment. Thank you for the opportunity to share our observations and concerns. As the largest not-for-profit program in Oregon supporting medication-assisted opioid recovery, my program serves nearly 700 total individuals. I see the power of opioid replacement therapy every day. I know that without it, Oregonians in need of this treatment would almost certainly be caught in greater personal suffering that would also increase health care, criminal justice, and additional social service costs. Thank you for your work to establish science-based pharmacy rules, your continued support for methadone treatment, and for considering the current advancements to opioid therapies. I hope you will consider the evidence and conclude that diverse agents, used earlier in the natural history of the chronic disease of addiction will better serve individuals and better serve our population.

The need: Unduplicated admissions for individuals reporting opioids as their primary drug of choice has increased over the last 10 years, where admissions for other primary drugs has reduced, according to statistics from Oregon's monitoring system. National statistics suggest only 20% of heroin users and even fewer who abuse prescription opioids receive medication-assisted treatment.

Findings and field experience: Research tells us that individuals who are dependent on opioids are more likely to succeed in recovery if they are receiving *both* medications—to address the physiology of opioid dependence—*and* counseling to aid in building a lifestyle supportive of long-term recovery. For many years, Methadone was the only medication available to these individuals. Today, we have a variety of options; these options include Vivitrol, Suboxone, and Methadone. As providers, we know, as you do, that recovery is not one-size-fits-all, and neither are these medications. Individuals may respond differently to these medications based on the length of time and severity of dependence, the motivation to change, and the support of the environment.

The support: The National Institute of Drug Abuse, American Medical Association, American Society of Addiction Medicine, Institute of Medicine, and Office of National Drug Control Policy, among others, support the use of medications in addiction treatment.

In a consensus statement released in January 2013, the National Association of State Drug and Alcohol Directors recommended medications be made available to all individuals likely to benefit from them so they may achieve sustained recovery from alcohol and opioids.

Our recommendation: The committee's expectation of failure on both methadone maintenance and Suboxone prior to authorizing Vivitrol suggests that these medications are equally effective for all opioid dependent individuals. It hinders the provider's use of expertise in making the decision based on patient need and available recovery supports. Federal guidelines for enrollment in an opioid treatment program (OTP), where methadone and psychosocial treatments are provided, require evidence of an extended period of opioid dependence as well as previously unsuccessful attempts at treatment without methadone. Opioid dependence is associated with significant changes to brain structure and function, and the extent of these changes are correlated with the duration of the dependence (1). By not approving the use of Vivitrol until after methadone failure, individuals struggling with opioid dependence are essentially forced to progress in their addiction until they require a highly structured treatment setting, where daily monitoring is required. This requirement prohibits patients from accessing treatment until they have experienced significant psychosocial losses and increases the likelihood they will incur permanent damage to the brain.

An OTP is not an optimal treatment setting for many individuals due to its transportation and scheduling requirements, its high-risk and high-need population, and the misperceptions many hold. As stated above, barely 20% of opioid dependent individuals are receiving the evidence-based treatments that are most likely to support recovery. By maintaining this prior authorization requirement, the overwhelming majority of individuals currently dependent on opioids simply will not receive effective treatment because they are either unwilling or unable to adhere to the requirements of an OTP.

Use of Vivitrol in combination with a comprehensive program presents an opportunity to provide treatment to a broader range of opioid dependent individuals. Authorizing the use of Vivitrol without requiring failure on other approved medications will allow providers to treat the addiction sooner, allowing the individual opportunity for effective intervention before the addiction progresses to the point that so much is lost and so much damage is done.

Thank you for your time and consideration,

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Reference:

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November 11, 2013

Drug Use Research and Management
Oregon State University and the
Oregon Pharmacy & Therapeutics Committee
OSUPharm.DI@oregonstate.edu

Thank you for the opportunity to provide written comments on the New Drug Evaluation for VIVITROL® (extended-release naltrexone suspension for intramuscular injection) at the upcoming Oregon Pharmacy & Therapeutics meeting on November 21, 2013.

Alkermes is committed to helping patients suffering from mental illnesses, in particular substance use disorders. Alkermes manufactures and markets VIVITROL.

Our comments in the letter below pertain to the New Drug Evaluation (NDE) for VIVITROL, specifically on the proposed renewal criteria for the treatment of patients with opioid dependence. We hope that the Oregon P & T Committee will find our comments helpful. In summary we would like to make note of, and comment on the following:

- The current proposed renewal criteria for opioid dependence determined by maintained abstinence based on negative urine toxicology screen do not provide an overall assessment of VIVITROL treatment response and should not be the sole basis for continued treatment decisions. Alkermes would like to suggest the opioid dependence renewal criteria for VIVITROL be similar to that of the alcohol dependence renewal criteria.
- The VIVITROL NDE provided to the P&T Committee contains information regarding a Boxed Warning on Hepatotoxicity. In July 2013 the Boxed Warning on Hepatotoxicity was removed from the new FDA approved prescribing information based on accumulated clinical safety data.

Alkermes

VIVITROL – Renewal Criteria for Opioid Dependence

VIVITROL is indicated for the prevention of relapse to opioid dependence following opioid detoxification. Treatment with VIVITROL should be part of a comprehensive management program that includes psychosocial support.[1]

In the pivotal trial for VIVITROL for the treatment of adults with opioid dependence[1], the primary endpoint evaluated was the response profile for confirmed abstinence (negative urine drug test and no self-reported opioid use) during weeks 5-24, which was discussed in the VIVITROL NDE. It is important to note that per study protocol, data from weeks 1-4 were omitted from the efficacy analysis due to the expectation that patients might challenge the opioid blockade during that timeframe.[2,3]

VIVITROL treatment response and continued treatment decisions in opioid dependence should not be based on negative urine screens alone. Alkermes would like to suggest the opioid dependence renewal criteria for VIVITROL criteria be consistent with experience from clinical trials. We outline below additional considerations for the assessment of VIVITROL treatment response in opioid dependent patients.

An important factor to consider in assessing treatment response and continued treatment decisions is the potential re-establishment of physical dependence, or lack thereof. Results from the pivotal trial showed that VIVITROL-treated patients had 94% fewer naloxone -confirmed relapses to physical dependence to opioids compared to placebo-treated patients. Although relapse to physical dependence was a secondary endpoint, it confirmed a fundamental therapeutic benefit of VIVITROL. Continuous opioid blockade prevented patients from relapsing to physical dependence even in those patients who had a positive urine screen; additionally, these patients were able to remain in treatment (**Figure 1**: Relapse to Physical Dependence – Patient Dot Plot).[2,3]

It is critical that patients be given the opportunity of continuing therapy along with psychosocial counseling even in the event of a positive urine screen which might represent a single slip rather than a true relapse. As indicated in Figure 1, multiple patients in the VIVITROL group stayed in treatment successfully despite having positive urine drug screens – an advantage of VIVITROL therapy because the continuous opioid blockade can offer protection from opioid induced euphoria, and relapsing to physical dependence.

Figure 1: Relapse to Physical Dependence – Patient Dot Plot

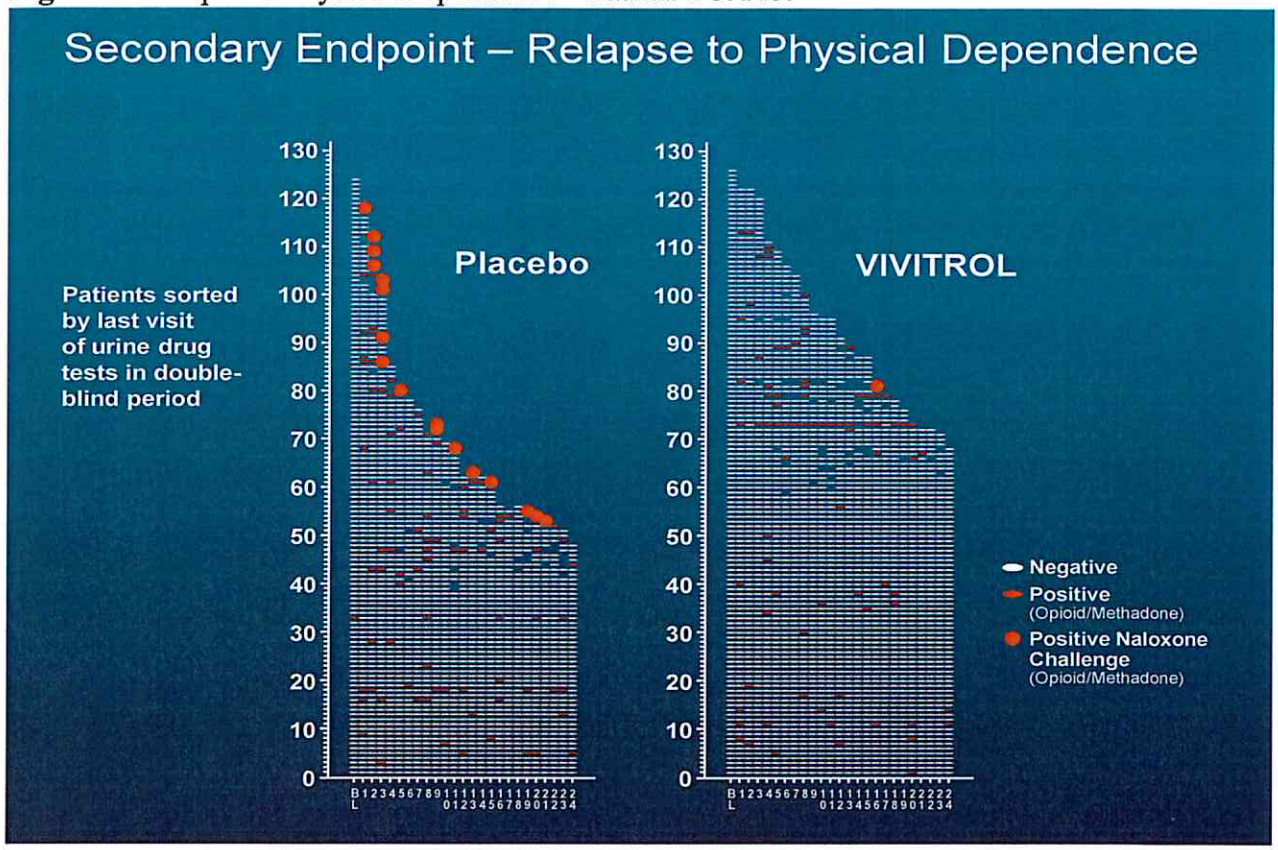

Figure 1. Description and Discussion:
Each horizontal line represents a single patient. Patients in each treatment group are stacked according to the number of urine samples provided. Patients with the most samples are on the bottom, moving to patients with the fewest samples on the top. The white ovals are opioid free samples. The orange ovals are non-opioid free samples. Where a dot is absent, no sample was provided, either due to discontinuation or missed study visit. The most prominent difference between VIVITROL and placebo, comes from fewer urine samples provided by placebo treated patients. This is due to the lower retention in treatment with placebo. There were 40% more opioid free weeks for VIVITROL versus placebo treated patients. When a positive urine test was observed, a naloxone challenge test was performed. The naloxone challenge test assesses for evidence of symptoms of withdrawal and highlights the distinction between opioid use and relapse. The orange circles indicate a positive naloxone challenge. Relapse to physiologic dependence was confirmed in one patient (patient missed two previous injections) in the VIVITROL-treatment arm and 17 in the placebo-treatment arm ($p<0.0001$).[2,3]

Additional measures to consider in determining a treatment response and continued treatment with VIVITROL include self reported opioid use, opioid craving and patient retention in treatment, all of which were secondary endpoints in the pivotal trial in opioid dependence. Patients in the VIVITROL group self reported a median of 99·2% (range 89·1–99·4) opioid-free days compared with 60·4% (46·2–94·0) for the placebo group (p=0·0004). The mean change in

craving as measured by self-report visual analogue scale of need for opioids was –10·1 (95% CI –12·3 to –7·8) in VIVITROL group compared with 0·7 (–3·1 to 4·4) in the placebo group ($p<0·0001$). Median retention was over 168 days in the VIVITROL group compared with 96 days (95% CI 63–165) in the placebo group ($p=0·0042$).

VIVITROL and Hepatotoxicity

At the time of approval, a Boxed Warning on hepatoxicity was placed in the VIVITROL label by the FDA due to studies reporting hepatic safety concerns with the administration of high doses of oral naltrexone (350 mg/d) or administration to patients with active liver disease.[4]

VIVITROL is an IM injection depot formulation that slowly releases naltrexone over approximately one month. It should be noted that the monthly naltrexone dose with VIVITROL is one fourth that of daily oral immediate-release naltrexone (380 mg vs. 1,500 mg/month). Since VIVITROL is an IM injection, naltrexone released from the intramuscular space avoids first pass hepatic metabolism and is associated with a greater area-under the curve for naltrexone and lower exposure to the principle active metabolite 6-β-naltrexone[5,6] than for 50 mg daily oral naltrexone.

Based on accumulated clinical safety data which included a large study in opioid dependent patients with chronic hepatitis C and HIV infection,[7] and adverse event reports submitted to the FDA, the FDA determined that the VIVITROL prescribing information should contain a Warning and Precaution related to potential hepatotoxicity, but not a Boxed Warning

We would like to thank you again for the opportunity to provide written comments on the New Drug Evaluation for VIVITROL (extended-release naltrexone suspension for intramuscular injection) at the upcoming Oregon Pharmacy & Therapeutics meeting on November 21, 2013. We hope you will find our comments related to the renewal criteria in opioid dependence and VIVITROL safety information helpful. If any additional information is needed, please feel free to contact me.

Kind Regards,

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