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Extended-release Naltrexone for Alcohol and Opioid Dependence: A Meta-Analysis of Healthcare Utilization Studies

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Abstract

Through improved adherence, once-monthly injectable extended-release naltrexone (XR-NTX) may provide an advantage over other oral agents approved 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. 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. We identified five observational studies comparing 1,565 patients using XR-NTX to other therapies over six months. Alcohol dependent XR-NTX patients had longer medication refill persistence versus acamprosate and oral naltrexone. Healthcare utilization and costs was generally lower or as low for XR-NTX-treated patients relative to other alcohol dependence agents. Opioid dependent XR-NTX patients had lower inpatient substance abuse-related utilization versus other agents and \$8170 lower total cost versus methadone.

1.0 Introduction

Alcohol and drug use disorders affect over 21 million Americans (8% of the US population) (*Substance Abuse and Mental Health Services Administration [SAMHSA]*, 2012) 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 (Berg et al., 2008; Howard, Arnsten, & Gourevitch, 2004; Mertens, Lu, Parthasarathy, Moore, & Weisner, 2003). 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 (Lindsey, Patterson, Ray, & Roohan, 2007). Studies consistently demonstrate appropriate treatment of substance abuse can reduce hospitalizations and emergency department (ED) utilization (Parthasarathy, Weisner, Hu, & Moore, 2001; Weisner, Mertens, Parthasarathy, Moore, & Lu, 2001). Despite this, alcohol dependence treatment ranks lowest in evidence-based practice among 25 health and behavioral health conditions (McGlynn et al., 2003).

The US government recommends pharmacotherapy as a standard of care in alcohol and opioid dependence (National Institute on Alcohol Abuse and Alcoholism [NIAAA], 2007; National Institute on Drug Abuse [NIDA], 2009) and the US 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 (Knudsen, Abraham, & Roman, 2011). 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 (Knudsen & Roman, 2012). Barriers to the use of medication include financing, medical staffing, logistical support, education and attitudes (Knudsen, Abraham, & Oser, 2011).

As in other chronic conditions (Bailey et al., 2012; Boswell, Cook, Burch, Eaddy, & Cantrell, 2012), medication adherence in substance abuse disorders is a major challenge to effective treatment (Gonzalez, Barinas, & O'Cleirigh, 2011; Weiss, 2004). 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 (Kranzler, Stephenson, Montejano, Wang, & Gastfriend, 2008). All currently approved agents are oral formulations intended for daily self-administration, except once-monthly, injectable XR-NTX (Gastfriend, 2011).

The Institute of Medicine identified substance use disorders as a high priority need for comparative effectiveness reviews (CERs) (Institute of Medicine [IOM], 2009) and CERs need to be regularly updated to optimize health care and policy decisions (Agency for Healthcare Research and Quality [AHRQ], 2012). 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 comparative cost and utilization impact of medicated treatment with XR-NTX in patients with these disorders.

2.0 Materials and 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 (Wells et al.). 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) (Cohen, 1988). We calculated unreported standard deviations based on reported p -values or 95% confidence intervals using established methods (J. Higgins & Green, 2011). 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 (J. P. Higgins & Thompson, 2002). The I^2 statistic is used in meta-analyses to quantify the proportion of total variation among studies that is due to heterogeneity rather than 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 (Sterne et al., 2011). All statistical analyses were conducted using Stata/IC 11.0 (StataCorp LP, College Station TX).

3.0 Results

3.1 Study Selection

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 (Baser, Chalk, Fiellin, & Gastfriend, 2011; Baser, Chalk, Rawson, & Gastfriend, 2011; Bryson, McConnell, Korthuis, & McCarty, 2011; Harris et al., 2012; Mark, Montejano, Kranzler, Chalk, & Gastfriend, 2010). Table 1

summarizes key study characteristics and study results. Four studies were retrospective cohort studies using administrative claims data from commercial health plans (Baser, Chalk, Fiellin, et al., 2011; Baser, Chalk, Rawson, et al., 2011; Bryson et al., 2011; Mark et al., 2010). Three studies (two in alcohol dependence and one in opioid dependence) compared patients receiving any pharmacotherapy to unmedicated patients (Baser, Chalk, Fiellin, et al., 2011; Baser, Chalk, Rawson, et al., 2011; Mark et al., 2010). 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 (Harris et al., 2012). Four studies examined alcohol dependence (Baser, Chalk, Rawson, et al., 2011; Bryson et al., 2011; Harris et al., 2012; Mark et al., 2010), and one examined opioid dependence (Baser, Chalk, Fiellin, et al., 2011).

Studies represented a mixture of both manufacturer-sponsored (Baser, Chalk, Fiellin, et al., 2011; Baser, Chalk, Rawson, et al., 2011; Mark et al., 2010) and independent research (Bryson et al., 2011; Harris et al., 2012). The NOS 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 (Baser, Chalk, Rawson, et al., 2011; Mark et al., 2010) and the opioid dependence study used instrumental variable analysis (Baser, Chalk, Fiellin, et al., 2011). 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 (Bryson et al., 2011). The VA study did not statistically adjust measures of adherence using baseline comorbidity variables (Harris et al., 2012).

3.2 Medication Refill Persistence

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) (Baser, Chalk, Fiellin, et al., 2011; Baser, Chalk, Rawson, et al., 2011; Bryson et al., 2011; Harris et al., 2012; Mark et al., 2010). For one study, we were able to obtain total days' supply dispensed for each drug from a co-author (Bryson et al., 2011). 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.

3.3 Detoxification Facility Use

Three studies analyzed inpatient detoxification facility utilization during the six months following the initial treatment (Baser, Chalk, Fiellin, et al., 2011; Baser, Chalk, Rawson, et al., 2011; Mark et al., 2010). 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.

3.4 Substance-abuse Related Inpatient Utilization

Four studies reported inpatient utilization for alcohol or opioid dependence (Baser, Chalk, Fiellin, et al., 2011; Baser, Chalk, Rawson, et al., 2011; Bryson et al., 2011; Mark et al., 2010) 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) (Bryson et al., 2011) and one reported only inpatient days while the others reported admissions (Mark et al., 2010). 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 (Bryson et al., 2011) 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 $-0.22 - 0.001$).

3.5 Emergency Department Utilization

Four studies reported ED visits (Baser, Chalk, Fiellin, et al., 2011; Baser, Chalk, Rawson, et al., 2011; Bryson et al., 2011; Mark et al., 2010). Because the study by Mark and colleagues (Mark et al., 2010) 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 $-0.08 - -0.01$).

3.6 Total Costs

Two papers reported the total of all inpatient, outpatient, addiction specialty, medical and pharmaceutical costs during the six months post index treatment (Baser, Chalk, Fiellin, et al., 2011; Baser, Chalk, Rawson, et al., 2011) and a third examined total costs excluding pharmacy (Bryson et al., 2011). 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 $-\$4482 - -\976). Excluding the Bryson et al. data (Bryson et al., 2011) did not substantially alter the result ($-\$3588$; 95% CI $-\$5396 - -\1780). In opioid dependence, XR-NTX patients had significantly lower total costs versus methadone ($-\$8170$; 95% CI $-12286 - -4054$).

3.7 Conversion to Clinical Metrics

Table 2 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 (Mark et al., 2010). 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.

3.8 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 (Baser, Chalk, Fiellin, et al., 2011; Baser, Chalk, Rawson, et al., 2011; Mark et al., 2010). Bryson and colleagues (Bryson et al., 2011) 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 (Baser, Chalk, Fiellin, et al., 2011), 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 (Baser, Chalk, Fiellin, et al., 2011; Baser, Chalk, Rawson, et al., 2011; Mark et al., 2010). 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 (Bryson et al., 2011) 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 $-0.92 - -0.85$) (Baser, Chalk, Fiellin, et al., 2011). Three studies reported total costs for any medication versus none (Baser, Chalk, Fiellin, et al., 2011; Baser, Chalk, Rawson, et al., 2011; Mark et al., 2010) and the Bryson

study (Bryson et al., 2011) 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.

4.0 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 (Pettinati et al., 2006), our analyses, in contrast, show relatively consistent cost and utilization reductions associated with use of XR-NTX. Our findings generally coincide with another study examining the association between oral naltrexone persistence and reduced healthcare service utilization (Kranzler et al., 2008). 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 (Cornish, Macleod, Strang, Vickerman, & Hickman, 2010), however, the Baser study of opioid dependence agents found a substantially shorter mean duration (Baser, Chalk, Fiellin, et al., 2011). Meanwhile, the optimal duration with extended antagonist therapy has not been specified and remains an individualized clinical decision.

4.1 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 (Schneeweiss & Avorn, 2005), 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. Four of five studies reflect a commercially insured population which may limit generalizability. 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 follow-up in all five studies was limited to six months and it remains unclear if effects are sustained beyond the study period. The ultimate duration of treatment for opioid and alcohol use disorders remains uncertain because clinical trial data for XR-NTX is limited to 12 to 24 weeks in duration. 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 (Institute of Medicine, 2009). Our analysis used real-world data from naturalistic community treatment, and included nearly 60,000 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. Clinical trials document the efficacy of pharmacotherapy (Mattick, Breen, Kimber, & Davoli, 2009; Mattick, Kimber, Breen, & Davoli, 2008; Rösner et al., 2010) and FDA-approved medications are available. National consensus standards, moreover, recommend pharmacotherapy (National Quality Forum, 2007) and both alcohol and opioid dependence can be successfully addressed in primary care settings (Sullivan, Tetrault, Braithwaite, Turner, & Fiellin, 2011). Finally, physicians have used XR-NTX successfully in both hospital and community-based general internal medicine practices (Lee et al., 2010).

Nonetheless, antipathy and ambivalence toward the use of medications to support recovery from alcohol and opioid dependence persist and reflect biases in philosophy of care, limited access to prescribers, a lack of training among prescribers and counselors, financing and licensing policies that inhibit use of medications, and perceptions that the cost of the medications is excessive (Knudsen, Abraham & Oser, 2011). The current average wholesale price of XR-NTX (\$1320 for one monthly injection; the Medicaid price is about 50% of the commercial price) constrains use. Other medications used for substance use disorders, however, are available generically and the relative high cost of XR-NTX may inhibit adoption for healthcare systems. Although the acquisition costs of XR-NTX are substantially higher than that of other agents, the evidence reviewed suggests off-setting reductions in other healthcare utilization producing either no net increase or reduced total costs of care. 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.

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The OHSU team (Hartung, Fu, McCarty) was responsible for study selection, data analysis, development of the first draft and figures.

References

- Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and Comparative Effectiveness Reviews Publication No. 10(12)-EHC063-EF. Rockville, MD: 2012. Retrieved from www.effectivehealthcare.ahrq.gov
- Bailey JE, Hajjar M, Shoib B, Tang J, Ray MM, Wan JY. Risk Factors Associated with Antihypertensive Medication Nonadherence in a Statewide Medicaid Population. *Am J Med Sci*. 2012;10.1097/MAJ.0b013e31825ce50f
- Baser O, Chalk M, Fiellin DA, Gastfriend DR. Cost and utilization outcomes of opioid-dependence treatments. *Am J Manag Care*. 2011; 17(Suppl 8):S235–248. [PubMed: 21761950]
- Baser O, Chalk M, Rawson R, Gastfriend DR. Alcohol dependence treatments: comprehensive healthcare costs, utilization outcomes, and pharmacotherapy persistence. *Am J Manag Care*. 2011; 17(Suppl 8):S222–234. [PubMed: 21761948]
- Berg KM, Kunins HV, Jackson JL, Nahvi S, Chaudhry A, Harris KA Jr, Arnsten JH. Association between alcohol consumption and both osteoporotic fracture and bone density. *Am J Med*. 2008; 121(5):406–418.10.1016/j.amjmed.2007.12.012 [PubMed: 18456037]

- Boswell KA, Cook CL, Burch SP, Eaddy MT, Cantrell CR. Associating Medication Adherence With Improved Outcomes: A Systematic Literature Review. *Am J Pharm Benefits*. 2012; 4(4):e97–e108.
- Bryson WC, McConnell J, Korthuis PT, McCarty D. Extended-release naltrexone for alcohol dependence: persistence and healthcare costs and utilization. *Am J Manag Care*. 2011; 17(Suppl 8):S222–234. [PubMed: 21761949]
- Cohen, J. *Statistical Power Analysis for the Behavioral Sciences*. Hillsdale, NJ: L. Erlbaum Associates; 1988.
- Cornish R, Macleod J, Strang J, Vickerman P, Hickman M. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. *BMJ*. 2010; 341:c5475.10.1136/bmj.c5475 [PubMed: 20978062]
- Gastfriend DR. Intramuscular extended-release naltrexone: current evidence. *Ann N Y Acad Sci*. 2011; 1216:144–166.10.1111/j.1749-6632.2010.05900.x [PubMed: 21272018]
- Gonzalez A, Barinas J, O'Cleirigh C. Substance use: impact on adherence and HIV medical treatment. *Curr HIV/AIDS Rep*. 2011; 8(4):223–234.10.1007/s11904-011-0093-5 [PubMed: 21858414]
- Harris AH, Oliva E, Bowe T, Humphreys KN, Kivlahan DR, Trafton JA. Pharmacotherapy of alcohol use disorders by the Veterans Health Administration: patterns of receipt and persistence. *Psychiatr Serv*. 2012; 63(7):679–685.10.1176/appi.ps.201000553 [PubMed: 22549276]
- Higgins, J.; Green, S. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. 2011. Retrieved from Available from www.cochrane-handbook.org
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002; 21(11):1539–1558.10.1002/sim.1186 [PubMed: 12111919]
- Howard AA, Arnsten JH, Gourevitch MN. Effect of alcohol consumption on diabetes mellitus: a systematic review. *Ann Intern Med*. 2004; 140(3):211–219. [PubMed: 14757619]
- Institute of Medicine. *Initial National Priorities for Comparative Effectiveness Research*. Washington, DC: The National Academies Press; 2009.
- Knudsen HK, Abraham AJ, Oser CB. Barriers to the implementation of medication-assisted treatment for substance use disorders: the importance of funding policies and medical infrastructure. *Eval Program Plann*. 2011; 34(4):375–381.10.1016/j.evalproplan.2011.02.004 [PubMed: 21371752]
- Knudsen HK, Abraham AJ, Roman PM. Adoption and implementation of medications in addiction treatment programs. *J Addict Med*. 2011; 5(1):21–27.10.1097/ADM.0b013e3181d41ddb [PubMed: 21359109]
- Knudsen HK, Roman PM. Financial factors and the implementation of medications for treating opioid use disorders. *J Addict Med*. 2012; 6(4):280–286.10.1097/ADM.0b013e318262a97a [PubMed: 22810057]
- Kranzler HR, Stephenson JJ, Montejano L, Wang S, Gastfriend DR. Persistence with oral naltrexone for alcohol treatment: implications for health-care utilization. *Addiction*. 2008; 103(11):1801–1808.10.1111/j.1360-0443.2008.02345.x [PubMed: 19032530]
- Lee JD, Grossman E, DiRocco D, Truncali A, Hanley K, Stevens D, Gourevitch MN. Extended-release naltrexone for treatment of alcohol dependence in primary care. *J Subst Abuse Treat*. 2010; 39(1):14–21.10.1016/j.jsat.2010.03.005 [PubMed: 20363090]
- Lindsey, M.; Patterson, W.; Ray, K.; Roohan, P. *Statistical Brief #3: Potentially Preventable Hospital Readmissions among Medicaid Recipients with Mental Health and/or Substance Abuse Health Conditions Compared with All Others*. Albany, NY: New York State Department of Health, Division of Quality and Evaluation, Office of Health Insurance Programs; 2007.
- Mark TL, Montejano LB, Kranzler HR, Chalk M, Gastfriend DR. Comparison of healthcare utilization among patients treated with alcoholism medications. *Am J Manag Care*. 2010; 16(12):879–888. [PubMed: 21348558]
- Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev*. 2009; (3):CD002209.10.1002/14651858.CD002209.pub2 [PubMed: 19588333]
- Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2008; (2):CD002207.10.1002/14651858.CD002207.pub3 [PubMed: 18425880]

- McGlynn EA, Asch SM, Adams J, Keesey J, Hicks J, DeCristofaro A, Kerr EA. The quality of health care delivered to adults in the United States. *N Engl J Med*. 2003; 348(26):2635–2645.10.1056/NEJMs022615 [PubMed: 12826639]
- Mertens JR, Lu YW, Parthasarathy S, Moore C, Weisner CM. Medical and psychiatric conditions of alcohol and drug treatment patients in an HMO: comparison with matched controls. *Arch Intern Med*. 2003; 163(20):2511–2517.10.1001/archinte.163.20.2511 [PubMed: 14609789]
- National Institute on Alcohol Abuse and Alcoholism. Helping Patients Who Drink Too Much: A Clinician's Guide (NIH Publication No. 07-3769. Rockville, MD: 2007. p. 1-34. Retrieved from http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.htm
- National Institute on Drug Abuse. Principles of Drug Addiction Treatment: A Research-Based Guide. Bethesda, MD: National Institute on Drug Abuse; 2009.
- National Quality Forum. National Voluntary Consensus Standards for the Treatment of Substance Use Conditions: Evidence-Based Treatment Practices. Washington, DC: National Quality Forum; 2007.
- Parthasarathy S, Weisner C, Hu TW, Moore C. Association of outpatient alcohol and drug treatment with health care utilization and cost: revisiting the offset hypothesis. *J Stud Alcohol*. 2001; 62(1): 89–97. [PubMed: 11271969]
- Pettinati HM, O'Brien CP, Rabinowitz AR, Wortman SP, Oslin DW, Kampman KM, Dackis CA. The status of naltrexone in the treatment of alcohol dependence: specific effects on heavy drinking. *J Clin Psychopharmacol*. 2006; 26(6):610–625.10.1097/01.jcp.0000245566.52401.20 [PubMed: 17110818]
- Rösner, S.; Hackl-Herrwerth, A.; Leucht, S.; Vecchi, S.; Srisurapanont, M.; Soyka, M. Opioid antagonists for alcohol dependence. *Cochrane Database of Systematic Reviews*. 2010. Retrieved from <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001867.pub3/abstract>
- Substance Abuse and Mental Health Services Administration. Results from the 2011 National Survey on Drug Use and Health: Summary of National Findings. Rockville, MD: 2012. Retrieved from <http://www.samhsa.gov/data/NSDUH/2k11Results/NSDUHresults2011.htm#2.16>
- Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J Clin Epidemiol*. 2005; 58(4):323–337.10.1016/j.jclinepi.2004.10.012 [PubMed: 15862718]
- Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, Higgins JP. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. 2011; 343:d4002.10.1136/bmj.d4002 [PubMed: 21784880]
- Sullivan LE, Tetrault JM, Braithwaite RS, Turner BJ, Fiellin DA. A meta-analysis of the efficacy of nonphysician brief interventions for unhealthy alcohol use: implications for the patient-centered medical home. *Am J Addict*. 2011; 20(4):343–356.10.1111/j.1521-0391.2011.00143.x [PubMed: 21679266]
- Weisner C, Mertens J, Parthasarathy S, Moore C, Lu Y. Integrating primary medical care with addiction treatment: a randomized controlled trial. *JAMA*. 2001; 286(14):1715–1723. [PubMed: 11594896]
- Weiss RD. Adherence to pharmacotherapy in patients with alcohol and opioid dependence. *Addiction*. 2004; 99(11):1382–1392.10.1111/j.1360-0443.2004.00884.x [PubMed: 15500591]
- Wells, GA.; Shea, B.; O'Connell, DJ.; Peterson, J.; Welch, V.; Losos, M.; Tugwell, P. [accessed 9/27/12] The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. undated from http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

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.

Table 1

Summary of study characteristics and outcomes for included studies. XR-NTX extended-release naltrexone. NTX-PO = oral naltrexone.

Author Year Population NOS Score	Population Databases	Treatments	Number Screened Enrolled	Age Sex Disease Severity Score (A vs B vs C vs D)	Confounder Adjustment Methods
Baser et al. Alcohol abuse 2011 NOS = 8	US Commercial Health Plans in PharMetrics Integrated Database and i3 Innovus	A. XR-NTX B. NTX-PO C. Acamprosate D. Disulfiram	Patients with 1 claim for any treatment = 204,133 A=661 B=2391 C=8958 D=3492 n= 15,502	NR in publication	Propensity score with weighting
Mark et al. Alcohol abuse 2011 NOS = 8	MarketScan Commercial Claims and Encounter Database of 150 large self-insured employers	A. XR-NTX B. NTX-PO C. Acamprosate D. Disulfiram	Patients with 1 claim for any treatment = 27,135 A=295 B=2064 C=5068 D=2076 n=9503	Age Groups: 18–34: 16% vs 16% vs 16% vs 16% 35–44: 23% vs 25% vs 25% vs 24% 45–54: 41% vs 37% vs 37% vs 37% 55–64: 21% vs 22% vs 22% vs 23% Pet Male: 53% vs 59% vs 59% vs 58% Charlson Score: 0.28 vs 0.24 vs 0.26 vs 0.26	Propensity score with inverse probability weighting
Bryson et al. Alcohol Abuse 2011 NOS = 7	Aetna Behavior Health Databases	A. XR-NTX B. NTX-PO C. Acamprosate D. Disulfiram E. Psychosocial	Patients with claim for EtOH use disorder = 73,292 A=211 B=1408 C=2479 D=1043 E=6374 n= 11515	Age: 42 vs 41 vs 45 vs 43 vs 39 Pet Male: 65% vs 53% vs 58% vs 60% vs 66% Charlson Score: 0.51 vs 0.44 vs 0.49 vs 0.37 vs 0.14	Difference-in-difference with multivariate regression
Baser et al. Opioid Abuse 2011 NOS = 8	US Commercial Health Plans in PharMetrics Integrated Database and i3 Innovus	A. XR-NTX B. NTX-PO C. Buprenorphine D. Methadone	Patients with 1 claim for any treatment = 220,917 A=156 B=845 C=7596 D=1916 n=10513	Age: 37 vs 34 vs 35 vs 42 Pet Male: 75% vs 59% vs 64% vs 51% Charlson Score: 0.22 vs 0.24 vs 0.26 vs 0.77 Elixhauser Score: 2.06 vs 2.05 vs 1.37 vs 2.0 5	Instrumental variable
Harris et al. Alcohol Abuse 2010 NOS = 7	National VHA administrative database	A. XR-NTX B. NTX-PO C. Acamprosate D. Disulfiram	Number screened not reported A=242 B=5811 C=1749 D=2977 N=10779	Demographics not reported	Not specified

Author Year Population NOS Score	Utilization: Pharmacy Adherence	Utilization: Outpatient/1000 Patients	Utilization: Inpatient/1000 patients	Costs: Outpatient/patient	Costs: Inpatient	Costs: Total
Baser et al. Alcohol abuse	A vs B vs C vs D PDC: 62% vs 50% vs 43% vs 46%	A vs B vs C vs D ED: 903 vs 817 vs 809 vs 823	A vs B vs C vs D	A vs B vs C vs D	A vs B vs C vs D	A vs B vs C vs D

Author Year Population NOS Score	Utilization: Pharmacy Adherence	Utilization: Outpatient/1000 Patients	Utilization: Inpatient/1000 patients	Costs: Outpatient/patient	Costs: Inpatient	Costs: Total
2011 NOS = 8		EtOH-related: 1758 vs 2153 vs 2483 vs 2311 Non-EtOH-related: 14,414 vs 12,726 vs 14,429 vs 13,159	Detoxification Days: 227 vs 361 vs 741 vs 429 EtOH Admissions: 82 vs 184 vs 317 vs 268 Non-EtOH Admissions: 109 vs 205 vs 343 vs 250	ED: \$272 vs \$227 vs \$209 vs \$227 EtOH-related: \$113 vs \$183 vs \$373 vs \$232 Non-EtOH-related: \$4510 vs \$3,444 vs \$3,589 vs \$3194	Detoxification or Rehabilitation Days: \$105 vs \$192 vs \$288 vs \$203 EtOH Admissions: \$474 vs \$618 vs \$1166 vs \$874 Non-EtOH Admissions: \$730 vs \$1091 vs \$3885 vs \$1498	\$6757 vs \$6595 vs \$10,345 vs \$7107 vs et al.
Mark et al. Alcohol abuse 2011 NOS = 8	A vs B vs C vs D PDC: 41% vs 37% vs 34% vs 37%	A vs B vs C vs D EtOH-related ED: 65 vs 57 vs 85 vs 82 Substance-abuse visits (mean): 3.81 vs 2.98 vs 3.09 vs 3.2	A vs B vs C vs D Detoxification Days: 224 vs 552 vs 525 vs 403 EtOH-related days: 137 vs 229 vs 435 vs 372 Non EtOH-related days: 869 vs 589 vs 697 vs 767	NR	A vs B vs C vs D Detoxification days: \$600 vs \$1479 vs \$1405 vs \$1079 EtOH-related days: \$382 vs \$641 vs \$1216 vs \$1041	A vs B vs C vs D NR
Bryson et al. Alcohol Abuse 2011 NOS = 7	A vs B vs C vs D PDC: 43% vs 35% vs 31% vs 30% *	A vs B, C, D ED: -70 vs -70 vs -120 Psychosocial Therapy Visits: 160 vs -80 vs 290 Behavioral Health Facility Visits: 170 vs -1020 vs -20	A vs B, C, D Total Admissions: -210 vs -220 vs -330 Total days: -1120 vs -1210 vs -1770	NR	NR	A vs B, C, D Non-Pharmacy Total Costs: -\$1309 vs -\$1798 vs -\$1513
Baser et al. Opioid Abuse 2011 NOS = 8	A vs B vs C vs D PDC: 34% vs 31% vs 38% vs 35%	A vs B vs C vs D ED: 608 vs 767 vs 1092 vs 1590 Opioid-related: 1397 vs 847 vs 1753 vs 693 Non-Opioid-related: 16654 vs 16338 vs 16840 vs 22054	A vs B vs C vs D Detoxification Days: 238 vs 300 vs 573 vs 269 * Opioid Admissions: 93 vs 145 vs 249 vs 198 Non-Opioid Admissions: 234 vs 387 vs 397 vs 561	A vs B vs C vs D ED: \$184 vs \$283 vs \$402 vs \$462 Opioid-related: \$124 vs \$273 vs \$184 vs \$74 Non-Opioid-related: \$4510 vs \$4068 vs \$3678 vs \$6173	A vs B vs C vs D Detoxification or Rehabilitation Days: \$216 vs \$193 vs \$219 vs \$264 Opioid Admissions: \$213 vs \$137 vs \$440 vs \$457 Non-Opioid Admissions: \$2003 vs \$3528 vs \$2290 vs \$7976	A vs B vs C vs D \$8582 vs \$8903 vs \$10,049 vs \$16,752
Harris et al. Alcohol Abuse 2012 NOS = 7	A vs B vs C vs D PDC: 45% vs 42% vs 39% vs 46%	NR	NR	NR	NR	NR

NOS=Newcastle-Ottawa Quality Assessment Scale, EtOH=Alcohol, ED=emergency department, NR=Not Reported

* data obtained from investigators

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Table 2

Summary of pooled estimates and clinical implications for studies of patients with alcohol use disorders.

Pooled Measure	Pooled Effect Estimates	Clinical Implication
Detoxification facility days ¹		Number needed to treat to reduce detoxification facility by 30 days
NTX-PO	NS	NS
Disulfiram	-201 days/1000 patients treated	149 patients
Acamprosate	-487 days/1000 patients treated	62 patients
Substance abuse-related inpatient days or admissions (SMD) ²		Number needed to treat to reduce substance abuse-related inpatient days by 30
NTX-PO	-0.10	51 patients
Disulfiram	-0.12	42 patients
Acamprosate	-0.11	46 patients
Inpatient substance abuse-related costs ¹		Number needed to treat to reduce inpatient substance-abuse costs by \$10,000
NTX-PO	-\$147/patient	68 patients
Disulfiram	-\$436/patient	23 patients
Acamprosate	-\$725/patient	14 patients
Total Costs ¹		Number need to treat to reduce total costs by \$10,000
NTX-PO	NS	NS
Disulfiram	NS	NS
Acamprosate	-\$2729/patient	4 patients

¹ Estimate rescaled to convey number of patients need to be treated to achieve a specific reduction in outcome

² SMD re-expressed as reduction in substance abuse-related inpatient days by multiplying SMD by pooled standard deviation for this measure provided by Mark et al. (5935). SMD*5935 = -x days per 1000 patients. This estimate was rescaled to convey number of patients need to be treated to achieve a specific reduction in outcome.

NS=not statistically significant