Accepted Manuscript

Extended-release naltrexone for alcohol and opioid dependence: A meta-analysis of healthcare utilization studies

Daniel Hartung PharmD, MPH, Dennis McCarty PhD, Rongwei Fu PhD, Katharina Wiest PhD, Mady Chalk PhD, David R. Gastfriend MD

Please cite this article as: Hartung, D., McCarty, D., Fu, R., Wiest, K., Chalk, M. & Gastfriend, D.R., Extended-release naltrexone for alcohol and opioid dependence: A meta-analysis of healthcare utilization studies, *Journal of Substance Abuse Treatment* (2014), doi: 10.1016/j.jsat.2014.03.007

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

Authors: *Daniel Hartung, PharmD, MPH[1]; Dennis McCarty, PhD[2]; Rongwei Fu, PhD[2]; Katharina Wiest, PhD[3]; Mady Chalk, PhD[4]; David R. Gastfriend, MD[5]

1.   Oregon State University / Oregon Health & Science University College of Pharmacy
        3303 SW Bond Avenue, CH12C, Portland OR 97239
        Email: hartungd@ohsu.edu; phone: 503-494-4720
2.   Department of Public Health and Preventive Medicine
        Oregon Health & Science University, CB669
        3181 SW Sam Jackson Park Road
        Portland, OR 97239
3.   CODA
        1027 E. Burnside St.
        Portland, OR 97214
4.   Treatment Research Institute
        Public Ledger Building
        Philadelphia, PA 19106
5.   Alkermes, Inc.
        852 Winter Street
        Waltham, MA 02451

Acknowledgments

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.

Table 1

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% Pct 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 Pct 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 Pct 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* 2.05 | 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 |

Table 1 continued

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 2011 NOS = 8	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 EtOH-related: 1758 *vs* 2153 *vs* 2483 *vs* 2311 Non-EtOH-related: 14,414 *vs* 12,726 *vs* 14,429 *vs* 13,159	A *vs* B *vs* C *vs* D 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	A *vs* B *vs* C *vs* D 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	A *vs* B *vs* C *vs* D 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	A *vs* B *vs* C *vs* D $6757 *vs* $6595 *vs* $10,345 *vs* $7107
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

Table 2

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

References

Agency for Healthcare Research and Quality. (2012). *Methods Guide for Effectiveness and Compartive Effectiveness Reviews Publication No. 10(12)-EHC063-EF*. Rockville, MD: Retreived from www.effectivehealthcare.ahrq.gov

Bailey, J. E., Hajjar, M., Shoib, B., Tang, J., Ray, M. M., & Wan, J. Y. (2012). Risk Factors Associated with Antihypertensive Medication Nonadherence in a Statewide Medicaid Population. *Am J Med Sci*. doi: 10.1097/MAJ.0b013e31825ce50f

Baser, O., Chalk, M., Fiellin, D. A., & Gastfriend, D. R. (2011). Cost and utilization outcomes of opioid-dependence treatments. *Am J Manag Care, 17 Suppl 8*, S235-248.

Baser, O., Chalk, M., Rawson, R., & Gastfriend, D. R. (2011). Alcohol dependence treatments: comprehensive healthcare costs, utilization outcomes, and pharmacotherapy persistence. *Am J Manag Care, 17 Suppl 8*, S222-234.

Berg, K. M., Kunins, H. V., Jackson, J. L., Nahvi, S., Chaudhry, A., Harris, K. A., Jr., . . . Arnsten, J. H. (2008). Association between alcohol consumption and both osteoporotic fracture and bone density. *Am J Med, 121*(5), 406-418. doi: 10.1016/j.amjmed.2007.12.012

Boswell, K. A., Cook, C. L., Burch, S. P., Eaddy, M. T., & Cantrell, C. R. (2012). Associating Medication Adherence With Improved Outcomes: A Systematic Literature Review. *Am J Pharm Benefits, 4*(4), e97-e108.

Bryson, W. C., McConnell, J., Korthuis, P. T., & McCarty, D. (2011). Extended-release naltrexone for alcohol dependence: persistence and healthcare costs and utilization. *Am J Manag Care, 17 Suppl 8*, S222-234.

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences*. Hillsdale, NJ: L.

Erlbaum Associates.

Cornish, R., Macleod, J., Strang, J., Vickerman, P., & Hickman, M. (2010). Risk of death during

and after opiate substitution treatment in primary care: prospective observational study in

UK General Practice Research Database. *BMJ, 341*, c5475. doi: 10.1136/bmj.c5475

Gastfriend, D. R. (2011). Intramuscular extended-release naltrexone: current evidence. *Ann N Y

Acad Sci, 1216*, 144-166. doi: 10.1111/j.1749-6632.2010.05900.x

Gonzalez, A., Barinas, J., & O'Cleirigh, C. (2011). Substance use: impact on adherence and HIV

medical treatment. *Curr HIV/AIDS Rep, 8*(4), 223-234. doi: 10.1007/s11904-011-0093-5

Harris, A. H., Oliva, E., Bowe, T., Humphreys, K. N., Kivlahan, D. R., & Trafton, J. A. (2012).

Pharmacotherapy of alcohol use disorders by the Veterans Health Administration:

patterns of receipt and persistence. *Psychiatr Serv, 63*(7), 679-685. doi:

10.1176/appi.ps.201000553

Higgins, J., & Green, S. (2011). Cochrane Handbook for Systematic Reviews of Interventions

Version 5.1.0 [updated March 2011]   Retrieved from Available from www.cochrane-

handbook.org

Higgins, J. P., & Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Stat

Med, 21*(11), 1539-1558. doi: 10.1002/sim.1186

Howard, A. A., Arnsten, J. H., & Gourevitch, M. N. (2004). Effect of alcohol consumption on

diabetes mellitus: a systematic review. *Ann Intern Med, 140*(3), 211-219.

Institute of Medicine (2009). *Initial National Priorities for Comparative Effectiveness Research.*

Washington, DC: The National Academies Press.

Knudsen, H. K., Abraham, A. J., & Oser, C. B. (2011). Barriers to the implementation of

medication-assisted treatment for substance use disorders: the importance of funding

policies and medical infrastructure. *Eval Program Plann, 34*(4), 375-381. doi:

10.1016/j.evalprogplan.2011.02.004

Knudsen, H. K., Abraham, A. J., & Roman, P. M. (2011). Adoption and implementation of

medications in addiction treatment programs. *J Addict Med, 5*(1), 21-27. doi:

10.1097/ADM.0b013e3181d41ddb

Knudsen, H. K., & Roman, P. M. (2012). Financial factors and the implementation of

medications for treating opioid use disorders. *J Addict Med, 6*(4), 280-286. doi:

10.1097/ADM.0b013e318262a97a

Kranzler, H. R., Stephenson, J. J., Montejano, L., Wang, S., & Gastfriend, D. R. (2008).

Persistence with oral naltrexone for alcohol treatment: implications for health-care

utilization. *Addiction, 103*(11), 1801-1808. doi: 10.1111/j.1360-0443.2008.02345.x

Lee, J. D., Grossman, E., DiRocco, D., Truncali, A., Hanley, K., Stevens, D., . . . Gourevitch, M.

N. (2010). Extended-release naltrexone for treatment of alcohol dependence in primary

care. *J Subst Abuse Treat, 39*(1), 14-21. doi: 10.1016/j.jsat.2010.03.005

Lindsey, M., Patterson, W., Ray, K., & Roohan, P. (2007). 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.

Mark, T. L., Montejano, L. B., Kranzler, H. R., Chalk, M., & Gastfriend, D. R. (2010).

Comparison of healthcare utilization among patients treated with alcoholism medications.

Am J Manag Care, 16(12), 879-888.

Mattick, R. P., Breen, C., Kimber, J., & Davoli, M. (2009). Methadone maintenance therapy

versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst

Rev*(3), CD002209. doi: 10.1002/14651858.CD002209.pub2

Mattick, R. P., Kimber, J., Breen, C., & Davoli, M. (2008). Buprenorphine maintenance versus

placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst

Rev*(2), CD002207. doi: 10.1002/14651858.CD002207.pub3

McGlynn, E. A., Asch, S. M., Adams, J., Keesey, J., Hicks, J., DeCristofaro, A., & Kerr, E. A.

(2003). The quality of health care delivered to adults in the United States. *N Engl J Med,

348*(26), 2635-2645. doi: 10.1056/NEJMsa022615

Mertens, J. R., Lu, Y. W., Parthasarathy, S., Moore, C., & Weisner, C. M. (2003). Medical and

psychiatric conditions of alcohol and drug treatment patients in an HMO: comparison

with matched controls. *Arch Intern Med, 163*(20), 2511-2517. doi:

10.1001/archinte.163.20.2511

National Institute on Alcohol Abuse and Alcoholism. (2007). *Helping Patients Who Drink Too

Much: A Clinician's Guide (NIH Publication No. 07-3769 (pp. 1-34 p)*. Rockville, MD.

Retrieved from

http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.

htm.

National Institute on Drug Abuse (2009). Principles of Drug Addiction Treatment: A Research-

Based Guide. Bethesda, MD: National Institute on Drug Abuse.

National Quality Forum (2007). National Voluntary Consensus Standards for the Treatment of

Substance Use Conditions: Evidence-Based Treatment Practices. Washington, DC:

National Quality Forum.

Parthasarathy, S., Weisner, C., Hu, T. W., & Moore, C. (2001). Association of outpatient alcohol

and drug treatment with health care utilization and cost: revisiting the offset hypothesis. *J*

Stud Alcohol, 62(1), 89-97.

Pettinati, H. M., O'Brien, C. P., Rabinowitz, A. R., Wortman, S. P., Oslin, D. W., Kampman, K.

M., & Dackis, C. A. (2006). The status of naltrexone in the treatment of alcohol

dependence: specific effects on heavy drinking. *J Clin Psychopharmacol, 26*(6), 610-625.

doi: 10.1097/01.jcp.0000245566.52401.20

Rösner, S., Hackl-Herrwerth, A., Leucht, S., Vecchi, S., Srisurapanont, M., & Soyka, M. (2010).

Opioid antagonists for alcohol dependence. *Cochrane Database of Systematic Reviews,*

(12). Retrieved from

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001867.pub3/abstract

doi:10.1002/14651858.CD001867.pub3

Substance Abuse and Mental Health Services Administration. (2012). *Results from the 2011*

National Survey on Drug Use and Health: Summary of National Findings (2012).

Rockville, MD. Retrieved from

http://www.samhsa.gov/data/NSDUH/2k11Results/NSDUHresults2011.htm#2.16.

Schneeweiss, S., & Avorn, J. (2005). A review of uses of health care utilization databases for

epidemiologic research on therapeutics. *J Clin Epidemiol, 58*(4), 323-337. doi:

10.1016/j.jclinepi.2004.10.012

Sterne, J. A., Sutton, A. J., Ioannidis, J. P., Terrin, N., Jones, D. R., Lau, J., . . . Higgins, J. P.

(2011). Recommendations for examining and interpreting funnel plot asymmetry in meta-

analyses of randomised controlled trials. *BMJ, 343*, d4002. doi: 10.1136/bmj.d4002

Sullivan, L. E., Tetrault, J. M., Braithwaite, R. S., Turner, B. J., & Fiellin, D. A. (2011). A meta-

analysis of the efficacy of nonphysician brief interventions for unhealthy alcohol use:

implications for the patient-centered medical home. *Am J Addict, 20*(4), 343-356. doi:

10.1111/j.1521-0391.2011.00143.x

Weisner, C., Mertens, J., Parthasarathy, S., Moore, C., & Lu, Y. (2001). Integrating primary

medical care with addiction treatment: a randomized controlled trial. *JAMA, 286*(14),

1715-1723.

Weiss, R. D. (2004). Adherence to pharmacotherapy in patients with alcohol and opioid

dependence. *Addiction, 99*(11), 1382-1392. doi: 10.1111/j.1360-0443.2004.00884.x

Wells, G. A., Shea, B., O'Connell, D. J., Peterson, J., Welch, V., Losos, M., & Tugwell, P.

(undated). The Newcastle-Ottawa Scale (NOS) for assessing the quality of

nonrandomised studies in meta-analyses, from

http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed 9/27/12)

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.

Table 1: Summary of study characteristics and outcomes for included studies. XR-NTX

extended-release naltrexone. NTX-PO = oral naltrexone.

Table 2: Summary of pooled estimates and clinical implications for studies of patients with
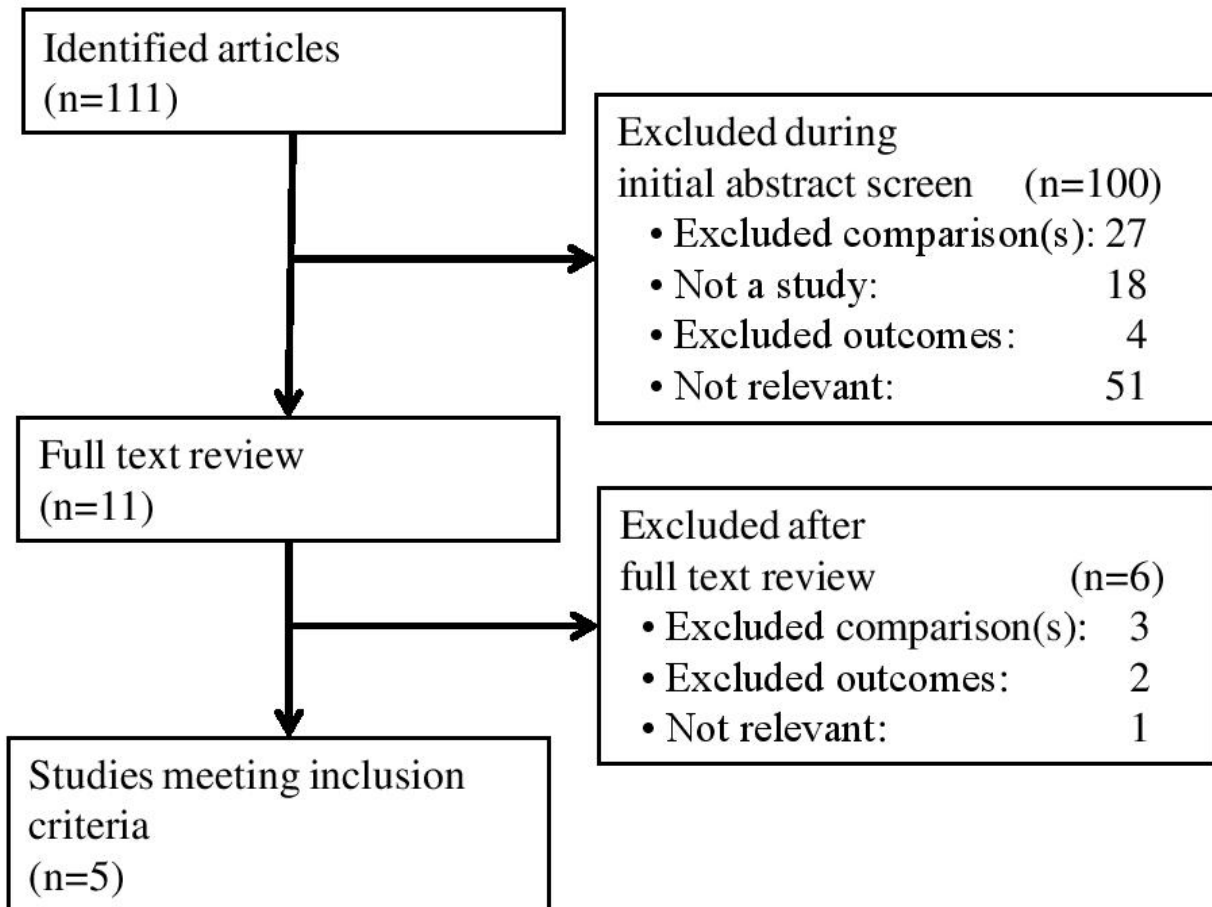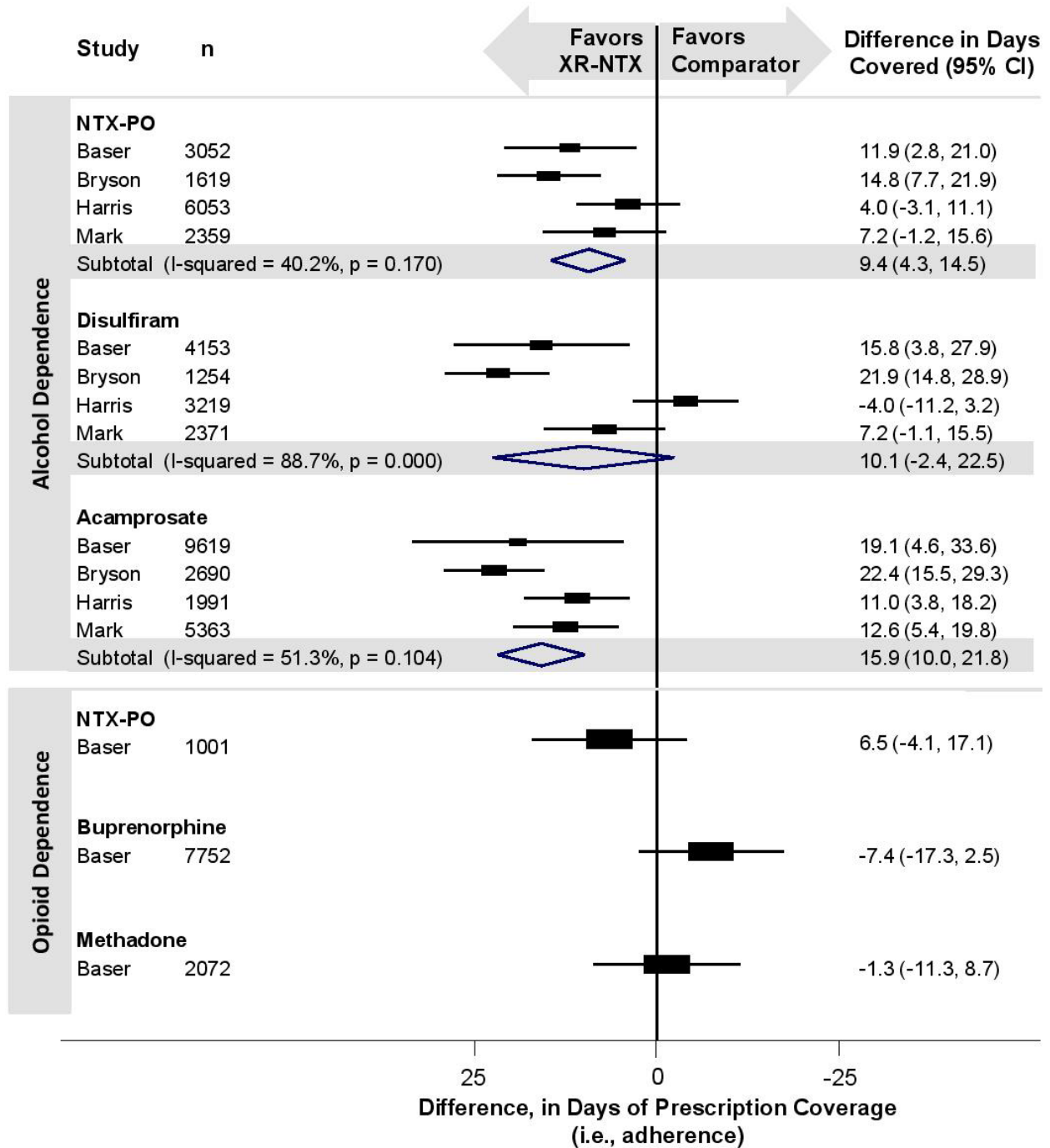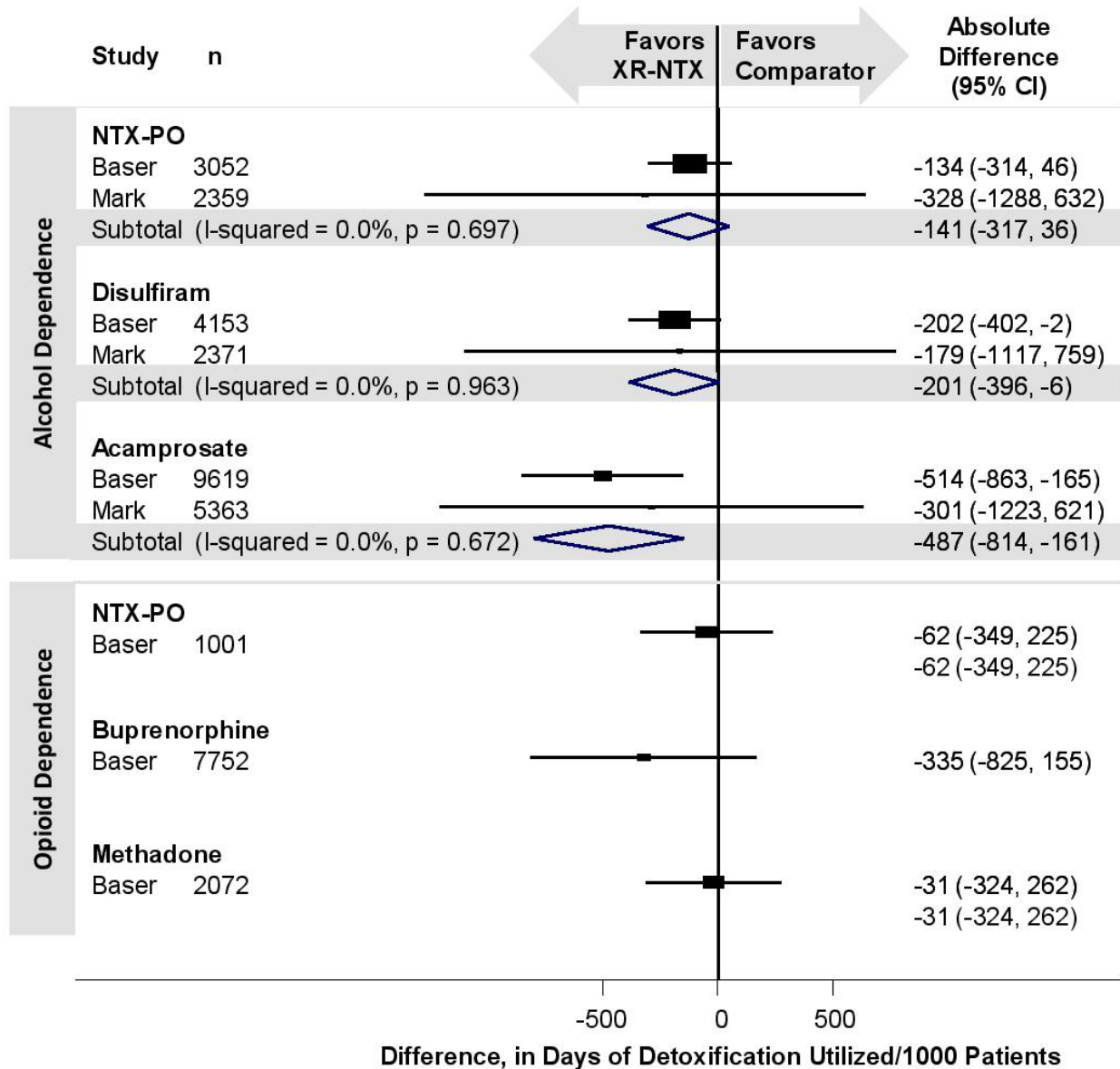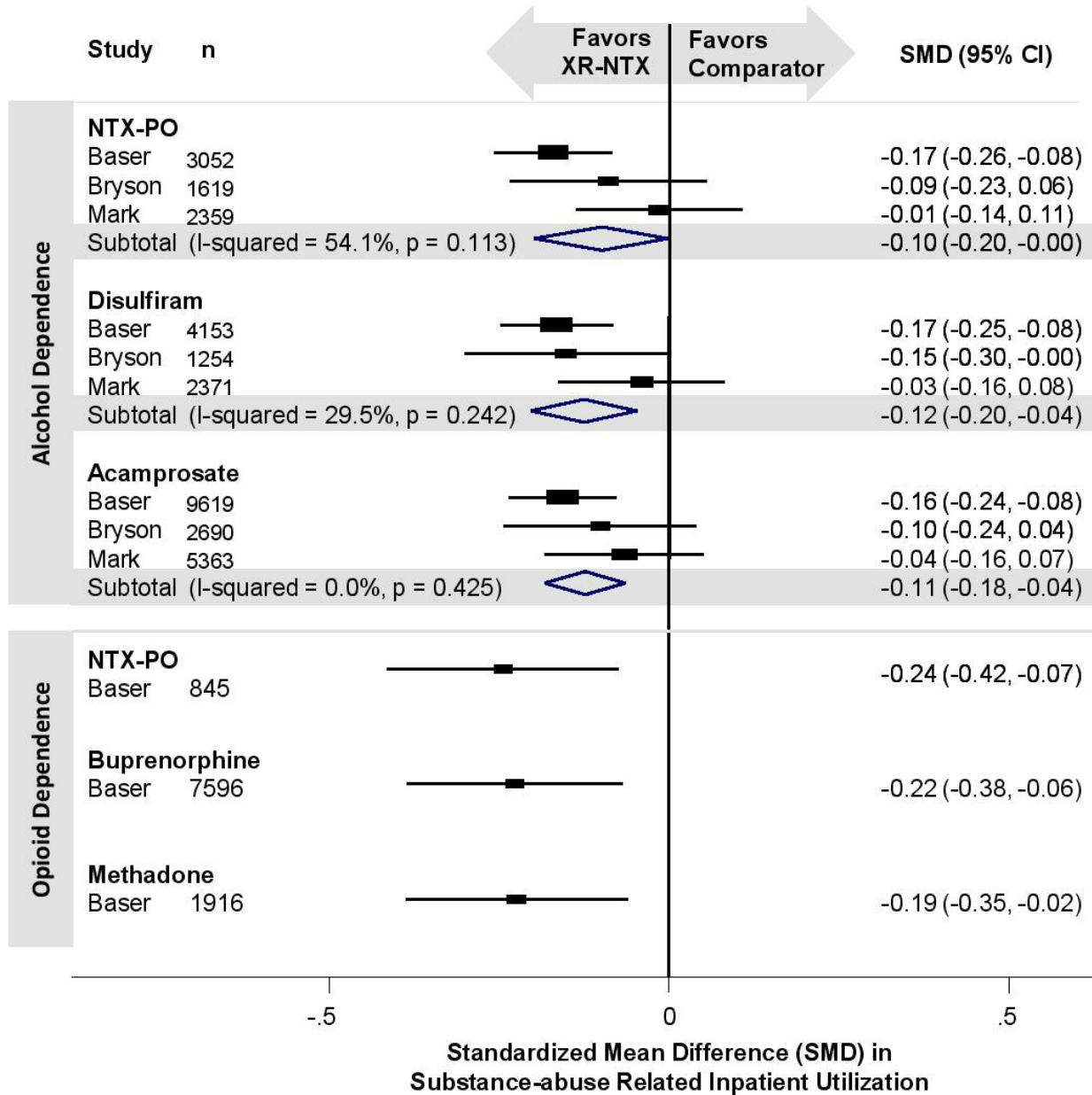
alcohol use disorders.

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5