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CONTINUING EDUCATION ACTIVITY

Long-Term Efficacy of Medication-Assisted Treatment of Opioid Addiction: A Systematic Literature Review—Part 2

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The purpose of this article is to examine the evidence on long-term efficacy of medication-assisted treatment for opioid addiction.

Learning Objectives/Outcomes: *After participating in this CME/CNE activity, the provider should be better able to:*

1. Describe the efficacy of full and partial opioid agonist medication-assisted treatment (MAT) in long-term patient outcomes.
2. Summarize the aggregate research evidence concerning the relative efficacy of methadone versus buprenorphine/buprenorphine-naloxone MAT on long-term patient outcomes.
3. Explain the research evidence for the efficacy for injectable antagonist MAT on long-term patient outcomes.

Key Words: Agonist pharmacotherapy, Buprenorphine, Medication-assisted treatment, Methadone, Naloxone, Opioid addiction

This article is the second of a 2-part series describing the results of a systematic literature review investigating the efficacy of medication-assisted treatment (MAT) for opioid addiction.

In This Issue

Part 1 described the epidemiology of opioid addiction in the US and provided a summary of the aggregate research evidence concerning the efficacy of full (methadone) and partial (buprenorphine) opioid agonist medications in comparison

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to traditional abstinence-focused psychotherapies. In this part 2, we describe and synthesize the results of a systematic literature review of the research evidence comparing the efficacy of methadone and buprenorphine MAT on long-term patient outcomes (as measured by treatment retention and drug-abstinence rates). The review also describes evidence concerning the efficacy of opioid antagonist pharmacotherapy, using either the oral or injectable formulation of the μ-opioid receptor antagonist naltrexone.

By addressing studies that measured long-term patient outcomes (defined as outcome measures ≥24 weeks), this article intends to inform management of opioid addiction as a chronic neuropsychiatric disease requiring ongoing treatment.

Results

Agonist Medication Efficacy Comparisons

An early 1993 investigation by Kosten et al[1] compared the efficacy of low-dose (2 mg/d) and high-dose (6 mg/d) sublingual buprenorphine with low-dose methadone (35 mg/d) and high-dose methadone (65 mg/d) in the treatment of 125 opioid-dependent individuals over a period of 24 weeks. The outcome measures used to operationalize treatment outcomes, treatment retention rate, and opioid use (assessed by weekly urinalysis testing), using an intention-to-treat (ITT) analysis, demonstrated that both high- and low-dose methadone treatments produced a significantly greater decrease in days of opioid use per month from baseline (29 d/mo) to month 6, 1.7 days (65 mg) and 2.8 days (35 mg) relative to high 4.0 days (6 mg) and low

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6.6 days (2 mg) dose buprenorphine.[1] Additionally, the percentage of opioid-negative urinalyses was significantly greater in the methadone (51%) versus buprenorphine (26%) treatment conditions, with high-dose (65 mg/d) methadone resulting in the highest rates of opioid-negative urinalyses (60%–80% range) after week 5 of treatment.[1]

A subsequent clinical trial investigated the relative efficacy of buprenorphine (8–16 mg/d) (n = 84) and methadone (50 mg/d) (n = 80) treatment in opioid-dependent individuals over 24 weeks using a flexible dosing regimen up to week 16 of treatment. Outcome analysis of urinalysis results (3x week) indicated comparable efficacy for this higher dosage regimen of buprenorphine versus methadone: percent positive urine samples (55%) buprenorphine versus (47%) methadone with overall 6-month treatment retention rates (56%) not significantly different between groups.[2] This research design used a comparatively larger buprenorphine dose (mean = 8.9 mg/d), and comparable methadone dose (mean = 54 mg/d) to the earlier study, and demonstrated that increased dosage in both treatment conditions was associated with decreased opioid (but not cocaine) use.

A further open-label trial evaluated the comparative efficacy of buprenorphine (8 mg/d maximum) and methadone (dosage not limited) in a sample of 34 opioid-dependent individuals over 24 weeks.[3] This study recapitulated the earlier findings showing significantly greater (weeks 12–24) retention rates in the methadone (72.5%) versus buprenorphine (37.5%) patients ($P < 0.05$), although buprenorphine patients provided a greater proportion of opioid-negative urines, this did not reach statistical significance.[3] Further research within the same research sample by Fischer et al,[4] conducted in 1999, investigating the relative efficacy of buprenorphine (2–8 mg/d, n = 24) and methadone (80 mg/d, n = 31) over a 24-week treatment period was able to demonstrate that, for treatment completers, buprenorphine patients had significantly lower rates of opioid-positive urinalyses at month 6 (weeks 22–24) relative to patients treated with methadone completing treatment ($P = 0.044$), although relative retention rates ($P < 0.05$) and median treatment retention ($P = 0.03$) duration were again found to be significantly greater for patients treated with methadone versus buprenorphine patients.[4]

These findings were the first to suggest a dichotomy within treatment outcomes for buprenorphine versus methadone MAT that was related to treatment retention rates and abstinence outcomes. The study confirmed previous research that demonstrated superior efficacy of methadone maintenance pharmacotherapy on long-term treatment retention rates (measured out to 24 weeks), while suggesting that for the percentage of individuals who remain in treatment, opioid abstinence rates (as measured by urinalysis testing) were generally lower in patients treated with buprenorphine versus methadone.

A subsequent 2007 investigation by Kakko et al[5] of buprenorphine (8 mg/d) and methadone (60 mg/d) over 6 months using Pearson correlation coefficient (percentage of opioid-negative urinalyses/total urinalyses) demonstrated no significant differences in percentage of opioid-negative urinalyses (60.4%) buprenorphine versus (65.5%) methadone, although a nonsignificant trend toward improved treatment retention in patients treated with methadone was observed.[6] Similarly, efficacy comparisons of methadone maintenance treatment (MMT; 120 mg/d maximum), and a stepped care treatment approach using buprenorphine-naloxone (32 mg/d maximum) with transition to MMT if needed, found significant but comparable increases in the proportion of opioid-negative urinalyses to approximately 80% by month 6 ($P = 0.0003$) with no significant between-group differences ($P = 0.90$) or between-group differences in overall 6-month retention (78%).[5] Important differences should be noted, as this design measured urinalysis results as 6 1-month blocks, and allowed patients to transition from one study medication to the other if it was clinically necessary.

A 2005 study compared the relative efficacy of 3-times-a-week levo-α-acetylmethadol (LAAM) (n = 209) and daily MMT (n = 106) over 6 months using a flexible dosing regimen. The study showed that LAAM patients had significantly lower opioid-positive urinalyses rates during treatment (46% vs 60%, $P = 0.000$) and at 26-week follow-up (39.8% vs 60.2%, $P < 0.002$) relative to MMT patients.[7] A further multivariate regression analysis showed that benefits of LAAM were limited to patients remaining in treatment at week 26 ($P = 0.02$).[7]

The general findings of Kakko et al[5] were replicated in another clinical trial comparing methadone (44–50 mg/d) and buprenorphine (9–12 mg/d) over 6 months using a flexible dosing paradigm, with significant improvement in the rate of opioid use from baseline to 6 months (64%–31%) ($P = 0.00$) in both groups, better overall retention in the methadone group ($P = 0.42$), and comparable retention in treatment (methadone 19.3 weeks vs buprenorphine 18.6 weeks) between groups.[8] A supplementary finding of clinical significance was the demonstration that severity of opioid-withdrawal symptoms was strongly correlated with treatment dropout ($r = 0.70$, $P = 0.00$).[8] However, Pinto et al[9] failed to find significant differences in treatment retention or abstinence rates between individuals choosing 6 months of buprenorphine maintenance (n = 22) or methadone maintenance (n = 20).

The SUMMIT Trial[10] was a larger replication that compared methadone (mean maximum dose = 73.3 mg/d) (n = 227) and buprenorphine (mean maximum dose = 11.7 mg/d) (n = 134) on long-term outcomes (monthly urinalysis) using a flexible dosing regimen over 6 months.

The SUMMIT Trial produced dichotomous findings, as patients treated with methadone were more than 2 times as

likely to be retained in treatment, with 6-month retention rates of 69.6% (methadone) versus 42.5% (buprenorphine). Conversely, among patients who were retained in treatment, buprenorphine patients were significantly more likely to suppress opioid use and achieve detoxification for patients completing 6 months of treatment.[10]

Recognition of the abuse potential of buprenorphine led to the formulation of combination buprenorphine-naloxone sublingual tablets, which contain μ-opioid receptor partial agonist and full antagonist compounds in a 4:1 ratio. Orally administered naloxone has limited oral absorption, but it provides effective μ-receptor blockade in the event that the medication is crushed and injected.[11] Many recent studies have investigated the efficacy of buprenorphine-naloxone relative to buprenorphine or methadone as maintenance therapies.

A 4-week randomized controlled trial was conducted to compare buprenorphine-naloxone (16 mg/4 mg/d) (n = 109), buprenorphine (16 mg/d) (n = 105), and placebo (n = 109) treatments in opioid dependence, with a subsequent 48-week open-label investigation of buprenorphine-naloxone combination treatment.[11] The trial demonstrated that the buprenorphine-naloxone combination and buprenorphine-only therapies each produced comparable and significant improvements in proportions of opioid-negative urinalyses relative to placebo (17.8%, 20.7%, and 5.8%, respectively) ($P < 0.0001$), whereas during the open-label phase percentages of biweekly opioid-negative urines were high.

Mintzer et al[12] showed that buprenorphine-naloxone treatment (8–24 mg/d) in a primary care setting (n = 99) had 54% of patients rated as "sober" at 6 months (sobriety was determined by physician judgment based on physical assessment and monthly urinalysis testing). In a different study of 17 opioid-dependent patients who were stable on buprenorphine treatment and were switched to unsupervised buprenorphine-naloxone treatment, 15 were retained in treatment at 6 months, with 5 patients having 1 or more opioid-positive urinalysis results.[13]

Investigation of outcomes for 53 opioid-dependent patients who had received buprenorphine-naloxone (24 mg/d maximum) in a primary care setting showed that the 2-year retention rate was 38% whereas 91% of urinalyses were negative for opioids.[14] These results are consistent with other evidence in addiction literature that demonstrates that outcomes remain good for patients who remain in treatment, and increased time in treatment is associated with improved long-term outcomes (in this case abstinence rates).

A larger study examining substitution of buprenorphine with buprenorphine-naloxone maintenance versus MMT demonstrated the noninferiority of buprenorphine-naloxone to methadone in treatment attrition rates, whereas buprenorphine-naloxone therapy patients had a significantly greater percentage of opioid-negative urinalyses.[15] These findings provide strong support for the efficacy of buprenorphine-naloxone pharmacotherapy, although the results should be interpreted with recognition of the nonrandomization of patients to treatment conditions.

A recent examination of the long-term outcomes after 2 to 5 years for patients from the START[16] clinical trial previously randomized to buprenorphine-naloxone or methadone for up to 24 weeks demonstrated no significant differences in mortality rates for buprenorphine-naloxone versus methadone. However, methadone demonstrated superiority to buprenorphine-naloxone on numerous long-term abstinence outcomes: Rates of opioid use at the 60-month follow-up were significantly greater in patients treated with buprenorphine-naloxone (42.8%) versus methadone (31.8%). Also, the percentage of positive urinalyses and past 30-day heroin use was significantly greater with buprenorphine-naloxone (5.8 days) versus methadone (4.4 days).[16] These results provided strong evidence in support of the superiority of methadone maintenance in long-term (60 months) outcomes for opioid-dependent individuals.

These aggregate findings illustrate some of the general trends that exist within the literature on comparative efficacy of these 2 agonist treatment interventions.

First, methadone maintenance has consistently been shown to lead to equal or superior outcomes in treatment retention rates relative to buprenorphine treatment,[1,3,4,9,16] although later studies using larger and more flexible buprenorphine dosing regimens demonstrated relatively better treatment retention outcomes.[4,5,8,15] This second factor illustrates a larger general trend within the research that indicated that, for both methadone and buprenorphine pharmacotherapies, increasing doses were consistently associated with improved treatment outcomes, and the best results were obtained when studies employed flexible dosing regimens tailored to individual patient characteristics (withdrawal or craving severity symptoms) that approximated the larger and more variable dosage regimens typically implemented in clinical addiction medicine. This flexibility, of course, represents a compromise in the rigor of the study design that has ramifications for the internal validity of the experimental designs that must be accounted for on an individual study basis.

The literature provided some support for improved abstinence rates in individuals treated with buprenorphine at relatively higher doses,[4,9,15] although other studies demonstrated superior abstinence rates with methadone treatment,[16] or demonstrated no significant between-group differences in abstinence outcomes.[5,6] The results illustrate the important point that interpretation of results across studies is complicated by both the method/frequency in which outcome results were operationally measured and the differences in medication dosages and flexibility of treatment regimens that were employed within the different research programs.

All of these factors should be considered when interpreting the differences in relative efficacy findings. Evidence has

accumulated for the efficacy and safety of the abuse-deterrent formulation of buprenorphine-naloxone in comparison to buprenorphine and MMTs.[11-13,15] The decreased risk of misuse and overdose associated with buprenorphine-naloxone supports its implementation as an alternative treatment modality for opioid addiction.

Pharmacologic Adjuncts for Agonist Treatment

An interesting study compared the efficacy of buprenorphine + clonidine (0.3 mg/d) and buprenorphine for 14 weeks after 6 weeks of supervised buprenorphine treatment using urinalyses and ecological momentary assessment (EMA) to assay treatment outcomes.[17] This study used an ITT analysis and demonstrated that buprenorphine + clonidine produced significantly greater abstinence duration relative to placebo, although differences between buprenorphine + clonidine and buprenorphine were not significant. Clonidine significantly increased the time to first lapse (defined as single-episode use) but had a nonsignificant effect on time to relapse (≥2 consecutive lapses).[17] EMA data analysis demonstrated that clonidine treatment was effective in partially decoupling stress from drug craving, and this result was reflected in a decreased likelihood of stress-associated craving. These results suggest potential avenues for individualized MAT therapies and potential novel pharmacotherapy adjuncts (α-adrenergic agonists) for agonist maintenance therapies.

Research on Influence of Patient Variables

A final area of research on agonist pharmacotherapies concerns research investigations that examined patient demographic variables affecting agonist treatment efficacy and secondary analyses of clinical trial data. Some investigations have sought baseline patient characteristics or treatment factors that were predictive of successful outcomes in MAT clinical trials.

Dreifuss et al[18] conducted a secondary analysis of the POATS Suboxone Clinical Trial, which identified baseline variables that were significant predictors of success for individuals addicted to prescription opioids. These variables included increased age, a lifetime diagnosis of major depressive disorder, negative history of parenteral opioid use, and negative history of prior addiction treatment episodes.

A further secondary analysis of the POATS trial[19] data assessed whether baseline severity factors (history of heroin use, presence of chronic pain) moderated the relationship between behavioral interventions and treatment outcomes, demonstrating that patients with a history of heroin use were significantly more likely to obtain successful (abstinence) outcomes with opioid treatment program counseling versus standard medical management if they were more than 60% adherent to the treatment regimen ($P = 0.03$).[19]

A secondary analysis of a large clinical trial where patients received buprenorphine-naloxone or methadone over 24 weeks confirmed methadone maintenance was associated with significantly greater treatment retention. Higher methadone dosage (>60 mg/d) was associated with highest treatment retention rates (>80%), whereas buprenorphine-naloxone retention rates increased linearly up to 60% at doses of 30 to 32 mg/d. Increased medication dosage was significantly associated with decreased opioid use.[20]

A secondary analysis of treatment outcomes for a 16-week program of buprenorphine treatment and behavioral treatment stratified patients into 3 different abuse categories. The analysis demonstrated that treatment outcomes were significantly better for prescription opioid users (70% opioid-negative urinalyses) relative to heroin (38%) and combined use (40%) groups over the treatment period.[21] These differences remained significant at follow-up week 42 but not week 52.[21]

A secondary analysis of naloxone induction trajectories and treatment outcomes in the START trial suggested that an increase in days needed to reach maintenance buprenorphine dose was significantly associated with increased month 6 opioid use.[22] Mitchell et al[23] performed a secondary analysis of changes in quality-of-life (QOL) indicators and treatment outcomes for African Americans over 6 months of buprenorphine treatment. The analysis failed to find significant associations between urinalysis results and QOL changes, but reported that self-reported opioid use was negatively associated with the scale score for psychological QOL.

Secondary analyses of agonist clinical research trials have provided important information about patient variables that are useful for stratifying individuals based on addiction severity phenotypes. Consistent evidence has accumulated for increased clinical severity and worse treatment outcomes for individuals with a history of heroin versus prescription drug abuse and a history of parenteral opioid abuse.[18,19,21] The analysis also identified factors associated with improved treatment outcomes, such as increased age and lack of previous episodes of addiction treatment.[18]

Taken together, this information suggests the possibility of distinct endophenotypes within the broader epiphenomenon of opioid addiction. Further characterization of these mediating factors could potentially inform an individualized addiction medicine treatment paradigm that targets risk and resilience patient factors to improve treatment outcomes. The data on differential efficacy outcomes for different doses and induction trajectories for agonist pharmacotherapies[20,22] provide further evidence in support of the existence of distinct addiction endophenotypes relating to pharmacogenetic factors. If these endophenotypes exist, they could be identified and targeted in future pharmacotherapies.

Antagonist Research

The National Institutes of Drug Abuse identified naltrexone as a potential pharmacotherapeutic intervention for opioid addiction disease in the 1970s. Orally administered naltrexone

was approved by the FDA for the treatment of opioid dependence in 1984. The lack of widespread implementation of antagonist opioid pharmacotherapies was largely the result of the high attrition rates for orally administered naltrexone, due to poor compliance.

Subsequent research involved the investigation of parenteral naltrexone therapies, which were hypothesized to provide more stable therapeutic serum blood levels and circumvent the difficulties associated with orally administered naltrexone (poor medication compliance and high relapse rates) through providing a stable and long-lasting blockade of μ-opioid receptors. To this date, much of the research on naltrexone has taken place within Russia, likely due to the fact that agonist (methadone maintenance) treatments were illegal there, necessitating alternative treatment interventions for opioid addiction.

Oral Antagonists

An early open-label trial investigated the efficacy of orally administered naltrexone + fluoxetine (50 mg/20 mg/d) and orally administered naltrexone + placebo in an 6-month trial, finding that 6- and 12-month retention rates were significantly better for patients treated with both naltrexone and fluoxetine.[24] These results were not replicated in a subsequent trial that examined abstinence rate outcomes in 280 opioid-dependent patients. The patients had been randomized to 6 months of MAT therapy, treated with 1 of 4 possible medication combinations: naltrexone + fluoxetine, naltrexone + placebo, placebo + fluoxetine, or placebo + placebo. The results demonstrate that patients treated with naltrexone had superior outcomes to patients in the nonnaltrexone groups, and that fluoxetine treatment did not produce significant improvements in treatment outcomes.[25]

A subsequent double-blinded clinical trial comparing orally administered naltrexone and biweekly counseling with placebo and biweekly counseling in 52 opioid-dependent individuals over 6 months demonstrated no significant differences in percentage of opioid-negative urinalyses between treatment groups, although naltrexone was associated with significantly greater 6-month retention and lower relapse rates.[26]

A trial comparing standard dose (50 mg/d), low-dose (0.5 mg/d), and ultra-low-dose (0.05 mg/d) orally administered naltrexone after 1 week of standard (50 mg/d) naltrexone therapy in 46 opioid-dependent patients over 6 months failed to find significant between-group differences in treatment retention rates, or significant relationships between abstinence rates and naltrexone dose or opioid use and dose.[27]

Subsequent investigations have incorporated various psychosocial or behavioral interventions into orally administered naltrexone therapy to ascertain whether these adjuncts improve treatment outcomes, with largely mixed results. Fals-Stewart and O'Farrell[28] investigated the relative efficacy of orally administered naltrexone, provided with either a combination of behavioral family counseling (BFC) and individual treatment, or with independent behavioral treatment alone, over 24 weeks, and found that BFC treatment significantly improved opioid abstinence rates during treatment. Nunes et al[29] tested the combination of orally administered naltrexone therapy and a behavioral adjunct [behavioral naltrexone therapy (BNT)] in comparison to naltrexone plus conventional therapy (CE), with results that suggested BNT improved treatment retention. However, there were no significant differences in urinalyses results, and treatment attrition was extremely high.

An investigation of orally administered naltrexone (300 mg/wk) and psychosocial counseling or psychosocial treatment-as-usual (TAU) did not find significant differences in treatment retention rates at 6 months.[30] Dunn et al[31] employed a clinical trial with patients randomized to either supervised orally administered naltrexone in a therapeutic workplace or take-home naltrexone and workplace access that was not contingent on observed medication compliance. The authors reported that observed improvements in medication compliance during the active therapy phase for therapeutic workplace contingency management patients did not persist at 12-month follow-up. The limited efficacy of orally administered naltrexone motivated research into the potential improvement of antagonist pharmacotherapy through sustained-release parenteral medication formulations.

Orally administered naltrexone has failed to demonstrate sustained efficacy in abstinence and retention outcomes, and these results are largely attributable to the short duration of antagonist blockade and poor treatment adherence, which makes relapse to opioid use extremely probable.[27-30]

Parenteral Antagonists

Parenteral opioid antagonist research has investigated subcutaneous implants and depot injectable formulations of naltrexone. An initial comparison of 12-month outcomes in patients treated with subcutaneous naltrexone implants or standard orally administered naltrexone therapy showed that implanted naltrexone patients had significantly higher retention compared with patients on orally administered naltrexone at 6 months (80% vs 42%) and 12 months (65% vs 17%).[32] Of those treated with implanted naltrexone, follow-up at months 18 and 24 showed that the rate of retention in treatment was 55.4% and 24%, respectively, with all treatment completers abstinent from opioids by urinalysis.

Building upon these significant results, subsequent investigations provided consistent evidence of the superiority of parenteral naltrexone pharmacotherapies over conventional orally administered naltrexone maintenance in improving long-term outcomes. An efficacy evaluation of a single (2.3 g) naltrexone implant and orally administered naltrexone (50 mg/d) over 6 months showed greater percentages of opioid-negative urinalyses for implant (49%) versus oral (21%) naltrexone patients and confirmed that more patients prescribed orally administered naltrexone had returned to regular heroin use by 6 months and at earlier timepoints.[33]

Further research investigating subcutaneous naltrexone implants has informed and supported this treatment modality. A 6-month trial comparing naltrexone implants to psychosocial TAU aftercare showed patients in the implant group had an average of 45 days less heroin use and 60 days less opioid use of the 6-month treatment period relative to control patients.[34] Kunoe et al[35] demonstrated that 56% of patients undergoing 6 months of treatment with a naltrexone implant challenged the opioid blockade during the treatment period (meaning that 44% remained opioid-abstinent at month 6). The overall mean days of opioid use per month decreased significantly from pretreatment baseline (mean 18 days) to month 6 (mean 6 days; $P = 0.001$).[35] However, within the treatment period, opioid use increased significantly over time from treatment month 1 to month 6. Krupitsky et al[36] provided strong research evidence for the superiority of implanted (1000 mg) versus orally administered naltrexone (50 mg/d) to significantly decrease the proportion of opioid-positive urinalyses relative to orally administered naltrexone or placebo ($P < 0.001$).

Parallel to these investigations, other research groups were investigating the potential of an injectable depot formulation of naltrexone that would be administered on a monthly basis. Krupitsky et al[37] provided the initial investigation, comparing the relative efficacy of injectable depot naltrexone (XR-NTX) (380 mg/inj) (n = 126) and placebo treatment over a 6-month period. In all measured outcomes, XR-NTX provided results significantly superior to placebo treatment. The median proportion urinalysis confirmed weeks of abstinence for XR-NTX was 90% versus 35% for placebo, whereas the numbers of patients with confirmed relapse to physiologic dependence were XR-NTX (1), placebo (17).

A subsequent investigation demonstrated superior efficacy and safety outcomes for XR-NTX naltrexone therapy (380 mg/mo) versus placebo in a 6-month clinical trial followed by an open-label trial of naltrexone for 1 year. Results of the open-label trial showed that completion rate was 62.3%, with 50.9% abstinent from opioids at all timepoints.[38] In addition, a pilot efficacy trial of 7 months of depot naltrexone during the transition from a correctional environment into the community in 27 opioid-dependent prerelease inmates demonstrated a retention rate of 37% at 7 months postrelease and indicated that individuals completing at least 6 injections were significantly less likely to have opioid-positive urinalyses than those who had fewer than 6 injections.[39]

An open-label 24-month trial of XR-NTX in opioid-dependent health care providers detoxified from opioids for at least 2 weeks examined long-term efficacy and safety.[40] The investigators found good results within this subpopulation; 21 (55.3%) patients received at least 12 months of XR-NTX injections and 14 (36.8%) patients completed the 24 monthly injections, whereas 5 discontinued after 1 injection. Among the 23 patients who did not complete all 24 injections, the median time to discontinuation was 183 days. Only 8 of the 519 monthly urinalyses (4 patients total) were positive for opioids. The authors reported no incidence of relapse, overdose, or death.[40]

The superior efficacy of depot XR-NTX treatment to psychosocial counseling in a 24-week treatment period was replicated in a population of inmates with lifetime history of opioid dependence.[41] Comparison of BNT + XR-NTX BNT + placebo, CE + XR-NTX, and CE + placebo in patients treated with orally administered naltrexone over 24 weeks uncovered a significant interaction between baseline severity and treatment condition. Low-severity patients had significantly higher retention rates (60%) in BNT + XR-NTX treatment condition ($P = 0.027$), whereas between-group differences were nonsignificant in higher-severity patients.[42]

Two studies investigated the therapeutic workplace contingency management paradigm as a behavioral adjunct to depot naltrexone and demonstrated that contingency management increased medication compliance and treatment retention, whereas opioid abstinence rates were not improved significantly.[43,44] An important finding uncovered during this research was that opioid-positive urinalyses were significantly more likely in patients with cocaine-positive urinalyses and that this effect was independent of the presence or absence of a therapeutic naltrexone μ-receptor blockade.[12]

Literature support for the efficacy of parenteral naltrexone treatments has provided significant evidence in abstinence and retention outcomes.[32,33,36,38,39]

The improved pharmacokinetics of depot naltrexone in producing a stable μ-opioid receptor blockade were reflected in improved retention rates and significant decreases in opioid use rates from pretreatment baseline.

The high-efficacy outcomes and monthly dosing regimen, combined with the lack of physiologic reinforcement of μ-opioid receptor activation, have made depot naltrexone an attractive treatment option for opioid addiction.

Kunoe et al[35] demonstrated that 56% of patients challenged the opioid receptor blockade during therapy, while opioid-use rates increased over the course of depot naltrexone treatment. These results suggest that a percentage of individuals continue to use opioids in the absence of physiologic reinforcement. Polysubstance use (cocaine) was associated with increased opioid use during naltrexone blockade.[43] It is therefore important that clinicians identify, diagnose, and treat polysubstance abuse. The potential of behavioral adjuncts to improve medication adherence could potentially comprise a comprehensive addiction treatment modality based on MAT and simultaneous vocational support for opioid-addicted individuals.

Antagonist Research Secondary Analyses

The remainder of the published literature on long-term outcomes in opioid antagonist research comprises secondary

analyses of clinical trial data and investigations of pharmacotherapeutic adjuncts to naltrexone maintenance treatment.

A secondary analysis by Hulse et al[45] of a clinical trial investigated serum naltrexone levels as a predictor of craving and relapse over 6 months of treatment with oral or implanted naltrexone. Effective therapeutic range of serum naltrexone was 1 to 3 ng/mL, with higher levels associated with decreased risk of opioid use. The odds of opioid use for patients with implanted naltrexone were significantly lower than those for patients prescribed orally administered naltrexone.[45]

A moderator analysis of a randomized controlled trial comparing XR-NTX and placebo treatment over 24 weeks dichotomized outcomes, with a positive outcome, demonstrated to be significantly more likely among XR-NTX versus placebo.[46] A 2013 study examining the α-2 adrenergic agonist guanfacine (0.3 mg/d) as an adjunctive therapy for orally administered naltrexone over 6 months failed to demonstrate a significant effect for guanfacine on treatment retention or percentage of opioid-negative urinalyses, although it was reported that guanfacine treatment decreased self-reported levels of stress and drug craving at later study timepoints.[47]

The aggregate evidence[45,46] demonstrates the inferiority of orally administered naltrexone therapy to parenteral antagonist treatments on long-term outcomes. The evidence for the efficacy of sustained-release formulations of naltrexone is much stronger. As a result, injectable depot naltrexone formulation was approved by the FDA for treatment of opioid dependence in 2011. Therapeutic drug levels need to be maintained during depot antagonist treatment to ensure optimal outcomes.[45] Evidence establishing the relative efficacy of agonist pharmacotherapies in compared with XR-NTX within different subpopulations with differing addiction phenotypes will be an important area of research.

Agonist-Antagonist Comparative Research

The initial literature review uncovered only 2 articles that compared the relative efficacy of agonist and antagonist pharmacotherapies. The primary research article by Schottenfeld et al[48] compared the relative efficacies of detoxification and counseling, counseling and agonist (buprenorphine), and counseling and antagonist (naltrexone) on long-term treatment outcomes after 24 weeks of therapy.

The study was intended to measure long-term outcomes, but was discontinued after 6 months due to the clearly demonstrated superior efficacy of buprenorphine treatment over both naltrexone and counseling treatments. Buprenorphine was significantly superior to naltrexone treatment in both days to first use and treatment retention rate.[48]

The second study was a secondary analysis of the primary study,[49] which demonstrated that buprenorphine treatment was more effective and more costly than naltrexone treatment for all measured outcomes (including treatment retention and days to first use). The ongoing clinical trial identified in the initial literature review was subsequently included in the revised manuscript.[50] This research comprised a 24-week open-label clinical trial comparing differences in relapse-free survival between opioid-dependent individuals randomized to monthly XR-NTX or daily sublingual buprenorphine-naloxone. The sample participants were stratified by treatment location and severity, and the primary outcome measure was relapse-free survival during the 24-week study period.

The study results indicated that XR-NTX treatment involved a significant induction hurdle; fewer patients initiated XR-NTX (72%) versus buprenorphine-naloxone (94%).[50] The ITT analysis of all participants indicated that 24-week relapse events were significantly more frequent among XR-NTX-treated patients (65%) than among buprenorphine-naloxone-treated patients (57%).[50] ITT analyses also demonstrated significantly higher frequency of opioid-negative urinalyses and more opioid-abstinent days among buprenorphine-naloxone compared with XR-NTX-treated patients, and the number of opioid-negative urinalyses was significantly greater among the buprenorphine-naloxone versus XR-NTX group.[50]

The authors conducted a separate analysis of the successfully inducted patients undergoing MAT. Among successfully inducted individuals, 24-week relapse events for XR-NTX (52%) and buprenorphine-naloxone (56%) and opioid abstinence rates were not significantly different between groups.[50] The evidence from the 3 studies was not sufficient to draw generalizable conclusions on the relative efficacy of agonist and antagonist pharmacotherapies.

Conclusion

This systematic review was conducted to provide a synthesis of the evidence on the relative efficacy of full opioid agonist (methadone), partial opioid agonist (buprenorphine or buprenorphine-naloxone), and opioid antagonist (naltrexone) medically MAT on long-term outcomes, defined as opioid abstinence and/or treatment retention, in the treatment of opioid addiction.

The body of research literature on agonist medications suggests a dichotomy within treatment outcomes for buprenorphine versus methadone MAT treatment retention rates and abstinence outcomes. These findings generally hold true within the body of literature on long-term treatment outcomes in agonist pharmacotherapy, although important caveats must be considered.

The first caveat relates to the potential confound that is introduced within a number of the research designs by nonrandomization to treatment condition. That is, some of the later studies employ a quasiexperimental design, where individual treatment condition is determined by patient choice or clinical judgment of the treating physician.[9,10,15] This potentially introduces systematic bias into the treatment conditions, as the sample populations could be expected to differ in other factors that could bias the outcomes. This particular limitation is ethically unavoidable, given the studies were undertaken at

a time when both treatment conditions had demonstrated efficacy within certain clinical situations, and investigators could not ethically contravene patient and provider decision-making that was based on achieving the best outcome for the individual patient based on the available evidence.

A related concern involves the differential treatment attrition rates of methadone and buprenorphine therapies and whether these bias the results of relative abstinence rates.[6] It is conceivable that the difference in urinalyses outcomes favoring buprenorphine treatment is an artifact of systematic differences in the populations of participants who successfully complete agonist pharmacotherapy. The higher attrition rate within buprenorphine subjects could result in the population of treatment completers representing relatively higher-functioning individuals with less-severe addiction phenotypes who would be expected to engage in less opioid use—and thereby have better abstinence rates over the progression of the studies.[6]

Under these assumptions, buprenorphine might represent a treatment with particular efficacy for the subpopulation of higher-functioning addicts, those with less chronic- and severe-use histories that would be amenable to the lower interference (partial vs full opioid-agonist activity, and outpatient dosing vs daily clinic attendance) that buprenorphine therapy provides, as has been suggested in previous research.[12,14] These factors are best accounted for by controlling for important covariates within the study design and during statistical analyses by the researcher, and the clear identification of the type of analysis (ITT vs treatment completer) that is being conducted to allow the reader to account for these variables.

The results of the research investigations of naltrexone pharmacotherapy support the potential utility of this treatment as an alternative to traditional agonist therapies. The development of sustained-release formulations of naltrexone (particularly XR-NTX) has overcome the traditional shortcomings of oral agonist therapy (low medication compliance and high relative risk of relapse and overdose) through providing a stable and long-lasting blockade of μ-opioid receptors, preventing both the reinforcement (euphoria) associated with opioid relapse and the respiratory depression that comprises the main mortality risk associated with an opioid overdose.

This therapy is hardly perfect, as the research literature documents that many patients attempt to overcome the opioid receptor blockade with massive doses or powerful synthetic opioids such as fentanyl, putting them at severe risk of overdose mortality.[35] Additionally, the research by Lee et al[50] demonstrated that the period of abstinence (generally 7 days) required before initiating XR-NTX presents a significant induction hurdle that is not present in initiating agonist MAT pharmacotherapy. Similarly, the rates of polysubstance use (particularly cocaine, benzodiazepines, and marijuana) remain high within the treatment population treated with both agonist and antagonist pharmacotherapies.

It is therefore critical that future research be undertaken to address significant gaps in the opioid addiction literature. Foremost among these is the need for a rigorous program of research that compares efficacy outcomes for agonist versus depot antagonist maintenance pharmacotherapies to document variation in treatment outcomes over time, as opioid addiction has repeatedly proven to be a chronic, relapsing disorder, and as of yet no definitive evidence concerning an upper limit of maintenance treatment duration exists.

Outstanding issues involve the potential subpopulations of opioid-dependent individuals who might benefit from a particular MAT modality due to genetic and neurobiologic variables that mediate outcomes. The literature and the field of addiction medicine would benefit greatly from comprehensive longitudinal investigations of genetic and epigenetic phenomena that confer susceptibility to opioid addiction and should guide an individualized addiction medicine treatment paradigm in the coming years. ■

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1. **A 1993 study by Kosten et al[1] comparing low- and high-dose buprenorphine with low- and high-dose methadone demonstrated which one of the following?**
   A. Both low-dose and high-dose methadone treatments produced a significantly greater decrease in opioid use days compared with low- and high-dose buprenorphine.
   B. High-dose methadone produced a greater decrease in opioid use days compared with high-dose buprenorphine, but there was no significant difference in opioid use days between low-dose methadone and low-dose buprenorphine.
   C. Both high- and low-dose buprenorphine produced significantly greater decreases in opioid use days compared with high- and low-dose methadone.
   D. There were no significant differences in opioid use days between methadone and buprenorphine patient groups.
2. **In a 1999 research study comparing treatment with buprenorphine (2–8 mg/d) to methadone (80 mg/d) in 55 patients undergoing MAT, Fischer et al[4] demonstrated which one of the following?**
   A. Contradiction of earlier results; patients treated with buprenorphine had better treatment retention outcomes (higher treatment retention rates compared with patients treated with methadone).
   B. Patients treated with methadone had significantly higher overall treatment retention rates, but individuals on buprenorphine who completed the entire study had higher opioid abstinence rates.
   C. Patients taking buprenorphine had a significantly lower risk of experiencing an opioid overdose during the study period.
3. **Which one of the following statements best describes the results of the SUMMIT Trial, which compared long-term outcomes in patients treated with a flexible dosing regimen of buprenorphine or methadone for 6 months?**
   A. Patients treated with methadone had greater overall treatment retention and lower illicit opioid use rates during months 1 to 3 of the study but higher rates of illicit opioid use and lower treatment retention in months 4 to 6.
   B. Patients who were treated with buprenorphine were significantly more likely to complete treatment compared with patients treated with methadone.
   C. Patients treated with methadone were more than twice as likely to be retained in treatment. However, among patients who completed all 6 months of treatment, patients treated with buprenorphine were significantly more likely to achieve abstinence outcomes.
   D. Neither methadone nor buprenorphine treatment had a significant effect on decreasing illicit opioid use after 3 months.

4. Which one of the following statements is *false*?

A. Buprenorphine-naloxone is an abuse-deterrent formulation of agonist (buprenorphine) and antagonist (naloxone)—drugs that can block the opioid receptor if the medication is crushed or snorted, but which do not block the therapeutic effect of the medication (because oral absorption of naloxone is low).

B. Buprenorphine and buprenorphine-naloxone both demonstrated significantly better improvements in illicit opioid abstinence compared with placebo.

C. Buprenorphine was significantly more effective in increasing opioid abstinence compared with both buprenorphine-naloxone and placebo.

D. Both buprenorphine and buprenorphine-naloxone produced high rates of opioid-negative urinalyses during a 48-week open-label study.

5. Which one of the following statements best describes the results of the START clinical trial in patients treated with 24 weeks of buprenorphine-naloxone or methadone?

A. Although long-term mortality rates were not significantly different in patients treated with buprenorphine-naloxone or methadone, there was strong evidence for the superiority of methadone over buprenorphine-naloxone on long-term abstinence (60-month outcomes).

B. Overall mortality rates associated with buprenorphine-naloxone and methadone were not significantly different, and both medications had equal evidence for long-term efficacy over 60 months.

C. As long as patients completed the entire 24 weeks of MAT, there was no risk of overdose or relapse during the study follow-up period.

6. According to the aggregate results of the systematic review, which one of the following statements is *true*?

A. The research evidence clearly demonstrates that methadone always produces better treatment retention results compared with buprenorphine and/buprenorphine-naloxone. There is no relationship between dosage levels and treatment retention outcomes for methadone or buprenorphine and buprenorphine-naloxone.

B. Although early studies suggested that methadone produced better treatment retention outcomes, newer research with higher doses of buprenorphine and buprenorphine-naloxone shows these drugs reliably have better treatment retention outcomes than methadone.

C. MMT has shown equal or better results (increased treatment retention) compared with buprenorphine or buprenorphine-naloxone, and the body of evidence suggests that higher doses and flexible dosing regimens are associated with improved treatment retention outcomes for both methadone and buprenorphine or buprenorphine-naloxone.

7. Which one of the following statements *best* describes the evidence for the comparative efficacy of methadone and buprenorphine/buprenorphine-naloxone MAT on long-term abstinence outcomes?

A. Evidence is inconclusive. (Some studies demonstrated better abstinence outcomes for high-dose buprenorphine and buprenorphine-naloxone; some demonstrated better abstinence outcomes for methadone; and some demonstrated no significant differences among medications.)

B. Methadone treatment consistently produces better abstinence outcomes compared with buprenorphine or buprenorphine-naloxone.

C. Buprenorphine/buprenorphine-naloxone treatment consistently produces better abstinence outcomes compared with methadone.

D. Methadone produces better abstinence outcomes during early treatment (up to 3 months), but buprenorphine and buprenorphine-naloxone are more effective in long-term abstinence outcomes (>3 months of treatment).

8. Which of the following statements is *true*?

A. Orally administered naltrexone is widely prescribed in the US because patients treated with orally administered naltrexone for opioid addiction have a significantly lower risk of overdose compared with individuals treated with agonist MAT.

B. Use of orally administered naltrexone has been largely abandoned in the US because of poor compliance and high overdose risk with agonist MAT.

C. Orally administered naltrexone produces a stable blockade of the μ-opioid receptor that prevents opioid receptor activation by opioid agonists and prevents intoxication for up to 28 days after treatment.

D. Orally administered naltrexone was the first drug approved by the FDA to treat opioid addiction in 1967.

9. Which one of the following statements is *true*?

A. The X-BOT clinical trial (2018) demonstrated that parenteral naltrexone has superior long-term outcomes compared with agonist MAT.

B. Parenteral naltrexone has demonstrated significantly better long-term treatment outcomes compared with orally administered naltrexone and placebo.

C. Parenteral naltrexone has not demonstrated superior long-term treatment outcomes compared with orally administered naltrexone.

10. Which one of the following statements is *true*?

A. Induction (>7-day abstinence period before beginning parenteral naltrexone treatment) and polysubstance use among patients treated with antagonist and agonist MAT represent an unmet treatment need.

B. Many individuals on MAT continue to use illicit opioids or other drugs and should not receive ongoing MAT.

C. MAT is never effective when the patient is not also treated with counseling/psychotherapy. Patients should not start MAT unless counseling/psychotherapy also is being provided.