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# Medication assisted treatment with buprenorphine/naloxone or methadone: Comparitive outcomes in patients with an opioid addiction

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**ABSTRACT** A clinical decision report appraising Hser YI, Evans E, Huang D, et al. Long-term outcomes after randomization to buprenorphine/naloxone versus methadone in a multi-site trial. *Addiction*. 2016;111(4):695-705. https://doi.org/10.1111/add.13238 for a patient with addiction to prescription opioids.

***Keywords***: *medication assisted treatment, opioid, methadone, buprenorphine*

## Clinical Context

David Green (pseudonym) is a 54 y.o. male with an opioid use disorder, and a history of an alcohol use disorder with 1 year of sobriety. Mr. Green was first prescribed oxycodone for injuries from a car accident in his early 30s. Ever since his musculoskeletal injuries healed, he has struggled with an addiction to opioid analgesics. In order to sustain his addiction, over the years, Mr. Green has repeatedly engaged in self-harm in order to obtain new prescriptions. His addiction has strained his relationship with his wife and 2 teenage children, and diminished his productivity as a contractor. Desperate to mend his relationship with his family, and regain financial stability, Mr. Green wants to know about his options when considering medication assisted treatment for opioid addiction, namely whether buprenorphine/naloxone treatment offered at the clinic is as effective as methadone treatment.

## Clinical Question

Is buprenorphine/naloxone as effective as methadone in medication assisted treatment for prescription opioid use disorder?

## Research Article

Hser YI, Evans E, Huang D, et al. Long-term outcomes after randomization to buprenorphine/naloxone versus methadone in a multi-site trial. *Addiction*. 2016;111(4):695-705. https://doi.org/10.1111/add.13238.

## Related Literature

A search of PubMed was done using the following fields: methadone AND opioid AND (buprenorphine/naloxone OR buprenorphine-naloxone) AND (prescription OR oral OR analgesic OR analgesia) NOT (pregnant OR pregnancy)

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This search resulted in 210 articles. Filtering for clinical trials and full-text articles narrowed the results to 43 articles. Upon review of titles and abstracts, 5 articles directly compared the effectiveness of buprenorphine/naloxone and methadone in patients with an opioid use disorder.

Law et al. conducted a double-blind randomized controlled trial (RCT) from 1998-2000 at an outpatient specialist drug clinic in the UK, of 80 individuals with ⩽ 3 years of opioid dependency, as defined by DSM-IV. Patients underwent a short-term treatment program involving induction/stabilization on methadone or buprenorphine/naloxone, followed by detoxification. The main outcome measures were urine drug screens for opiates, and withdrawal and craving questionnaires. There were no overall differences in positive urine drug screens and drop-outs during any phase of the study. While this was a well-designed study, it was excluded because the induction/stabilization phase only lasted a brief period of 2-6 weeks, followed by a detoxification phase of 2.5 weeks, during which medication assistance, either with buprenorphine/naloxone or methadone was gradually withdrawn.[1]

Potter et al. conducted a randomized open-label study from 2006 to 2009 of 1269 patients randomized to receive either methadone or buprenorphine/naloxone. Participants completed a 24-week active medication phase, and treatment outcomes were opioid use during the final 30 days of treatment. This study was unique in that it's primary objective was to explore differences in opioid replacement therapy treatment outcomes by type (heroin, opioid analgesic [OA], or combined [heroin and OA]) and route (injector or non-injector) of opioid use. The study concluded that there is no evidence of superiority of buprenorphine/naloxone over methadone for opioid analgesic users. However, this study was excluded due to a lack of reported statistics to support the conclusions.[2]

Neumann et al. conducted an RCT in which 54 patients with chronic pain and opioid addiction were randomized to receive either buprenorphine/naloxone or methadone. At 6-month follow-up, both groups reported reduction in pain relative to baseline, but compared to 5 in the buprenorphine group, none in the methadone group reported illicit opioid use. While this was a well-designed study, it was excluded due to the small sample size. Additionally, the study focused exclusively on patients with existing chronic pain, which is not applicable to this clinical context.[3]

McKeganey et al. conducted a prospective cohort study comparing 71 individuals who were either on methadone or buprenorphine/naloxone. Results showed that when controlling for a number of patient-level covariates, both methadone and Buprenorphine/naloxone significantly reduced current users' days of heroin use between the 90 days prior to intake and at the 8-month follow-up, with buprenorphine/naloxone yielding a significantly larger magnitude reduction in heroin use days than methadone. This study was excluded because it used an observational rather than controlled study design, used a small sample size, and only included heroin users rather than patients dependent on opioid analgesics.[4]

Hser et al. conducted a follow-up from 2011–2014 of 1,080 opioid-dependent participants enrolled in opioid treatment programs in the USA between 2006 and 2009, randomized to receive open-label buprenorphine/naloxone or methadone for up to 24 weeks. Outcomes were mortality and opioid use. While mortality rates did not differ significantly between the two groups, opioid use at follow-up was higher among participants randomized to buprenorphine/naloxone relative to methadone. This study was ultimately selected because it was a rigorous RCT with a large sample size. Additionally, the sample group included patients using opioid analgesics and reported outcomes relevant to the patient context.[5] This article had the highest internal and external validity.

Using the SORT criteria, the Grade of Recommendation is B, based on consistent studies of mixed methodologies of fair methodological quality.[6]

## Critical Appraisal

Hser et al. performed a follow-up in 2011–2014 of 1,080 opioid-dependent participants entering 7 opioid treatment programs in the USA between 2006 and 2009 and randomized to receive open-label buprenorphine/naloxone or methadone for up to 24 weeks; 795 participants completed in-person interviews (~74% follow-up interview rate). Outcomes included mortality and continued opioid use.[5] Based on the Strength of Recommendations Taxonomy (SORT) criteria, this study would be classified as Level 2.[6]

The study authors carefully document demographic details for the 795 patients as follows: mean age at baseline was 37.4, 34.1% were female, 72.6% white, 11.2% Hispanic, 9.2% African American, and 7.0% other race/ethnicity. The two medication groups were

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all similar in baseline measures except that more participants in the methadone group reported cocaine use (37.2%) than in the buprenorphine/naloxone group (30.2%). While the demographic similarities between the groups suggests that randomization was successful and minimized selection bias, the tools and exact methods of randomization were not detailed in the paper. Because of higher dropout rate in the BUP group, the randomization protocol was changed from 1:1 to 2:1, favoring buprenorphine midway through the study. The study performed a sensitivity analysis to ensure that there were no differences in the demographic characteristics of participants included (n=795) and omitted (n=285) from analysis, to assess participation bias.[5] Yet, this is a significant loss of follow up precluding an intention to treat analysis, which was not attempted.

While the study was not blinded, outside of the treatment, both groups of patients were treated equally. Enrollment occurred during 2006-2009 and assessment occurred during 2011-2014 Using timeline follow back (TLFB). This was poorly described, leaving the reader with the impression that a single follow up interview was used to impute monthly rates over a five-year time interval, exposing the data to significant recall bias. Also not described is the fact that methadone requires daily supervised treatment, but the protocol for BUP was not described, leading the reader to wonder if the two groups were treated similarly or not. This introducing a large bias if the two groups were not treated similarly, particularly as this was an open label trial.

The study considered clinically relevant outcomes in patients being treated for opioid dependence disorders, namely mortality rates and continued opioid use.[5] However, the study may have been enhanced by consideration of patient-centered quality of life measures. While the average age of the patients in the study was slightly younger than that of our patient, the ethnic composition of the study subjects matches our patient.

There were 23 deaths in the buprenorphine/naloxone group (n=630, or 3.6%) and 26 deaths in the methadone group (n=450, or 5.8%); the difference was not statistically different (X2(1)=2.74; p=.10). The hazard ratio in the Cox regression that included covariates (age, gender, race/ethnicity, cocaine use at the baseline) showed no difference in time to death between the two randomized conditions (X2(1)=2.71; p=.10). Opioid use was higher among participants randomized to buprenorphine/naloxone relative to methadone at the follow-up interview. Opioid use was assessed by a positive urine test or self-reported past-30-day opioid use with significantly more opioid use among buprenorphine/naloxone than methadone participants (50.9% vs. 41.1%, effect size (h)=0.20 [0.06, 0.34]. While the difference in the percent of patients using opioids at the time of follow up was found to be statistically significant, it is not clear whether this result is clinically meaningful, when considering other factors such as cost and accessibility of each treatment.

## Clinical Application

Mr. Green is a middle-aged man who works as a contractor and has a young family with whom he would like to reconcile and maintain a healthy relationship. He primarily struggles with dependence on opioid analgesics, and has never used heroin or injection drugs. He also has no other comorbidities. While the study conducted by Hser et al. considered a sample population that included patients with dependence on opioid analgesics, they also considered individuals using heroin or a combination of the two, and the reported results were not stratified by patient type. Hser et al. found a statistically significant difference between buprenorphine/naloxone and methadone with more patients continuing to use opioids in the buprenorphine/naloxone group compared to methadone. However, the clinical significance of these result is less clear.

A recent systematic review by Srivastava et al. comparing research on methadone and buprenorphine/naloxone concluded that while methadone has higher treatment retention rates, buprenorphine/naloxone has a lower risk of overdose.[7] They conclude that ultimately, medication assisted treatment is superior to abstinence-based treatment and that patient characteristics should drive the decision between methadone and buprenorphine/naloxone. Srivastava et al. suggest that for patients at high risk of dropout (such as adolescents and socially unstable patients), treatment retention should take precedence over other clinical considerations. For patients with high risk of toxicity (such as patients with heavy alcohol or benzodiazepine use), safety would likely be the first consideration. Given that Mr. Green is relatively socially stable, and has a history of alcohol abuse, buprenorphine/naloxone would be favored over methadone. Furthermore, buprenorphine/naloxone is preferred over methadone in patients whose work or family responsibilities make it difficult to attend the pharmacy daily. Methadone programs dispense methadone, with its high risk of overdose, under daily supervision during the first

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few months of treatment. Alternatively, buprenorphine/naloxone can safely be dispensed as take-home doses earlier on in treatment if the patient is at low risk of diversion. Given the clinical context of our patient, buprenorphine/naloxone therapy seemed to be the more reasonable option. Mr. Green also particularly appreciated that he could receive buprenorphine/naloxone therapy from his primary care physician with whom he already has an established relationship.

## New Knowledge Related to Clinical Decision Science

Mr. Green had the opportunity to discuss his treatment options and access MAT because he happened to have established care with a primary care physician who was licensed to prescribe buprenorphine/naloxone. However, many patients face barriers to MAT due to few physicians prescribing buprenorphine and insurance prior authorizations that can delay or deny access to therapy.[8] In 2000, the Drug Addiction Treatment Act (DATA 2000) expanded access to treatment for opioid use disorder by legalizing office-based maintenance therapy.[9] To obtain a DATA 2000 waiver, physicians must notify the Substance Abuse and Mental Health Services Administration of their intent to begin prescribing this treatment, have a state medical license and a Drug Enforcement Administration number, and complete eight hours of training. Despite these efforts to make MAT more accessible in the primary care setting, physician uptake of buprenorphine has been limited for a number of reasons, including physician concerns about diversion, stigma toward substance use disorders, concerns about appropriate reimbursement, and time capacity.[10]

In 2016, 1.8 million Americans had a substance use disorder involving prescription pain medications.[11] Between 2000 and 2015, over 500,000 individuals died from opioid overdose, with deaths rising with prescription opioid sales.[12] As the largest prescribers of opioids, primary care physicians have an important role in reversing these trends.[13] In conjunction with continued use of methadone clinics, increasing the number of primary care physicians who prescribe buprenorphine is critical to making MAT more accessible for patients such as Mr. Green.

Questions raised using Clinical Decision Science change the type of questions and type of data needed to treat patients with opiate use disorder. Instead of focusing on patient level data, we need more physician level data. What are the drivers of uptake for MAT among providers? The body-politic has alternately blamed pharmaceutical companies—and physicians for creating an opioid use epidemic. What is the role of "courage" to engage patients that have a high-risk disorder? What risks are there to physician reputation? What difficulties prevent this treatment from becoming more widely available? This questions often can only be answered using social context data and analysis. This story began years ago and is currently evolving. Different clinical research is needed to help patients with this dangerous condition.

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