Impact of extended release naltrexone on health-related quality of life in individuals with legal involvement and opioid use disorders

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Abstract

Background: Understanding the impact of medications for opioid use disorder on health related quality of life (QOL) may help to explain why few individuals with legal involvement remain in treatment, specifically those receiving opioid antagonists. QOL is an established predictor of treatment retention and has been shown to improve with some treatment for opioid use disorder. Yet limited research has examined QOL with opioid antagonists. We examined the impact of extended release naltrexone (XR-NTX) on QOL and retention in treatment in a randomized, multi-site trial of individuals with legal involvement.

Methods: The participants were 308 community-dwelling adults with current or recent legal involvement with opioid dependence at five site across United States. They were randomized to receive XR-NTX or treatment as usual for 6 months. QOL was measured every 2 weeks using Euro QOL individual items, summary index score, and health state today metric.

Results: No significant difference in QOL scores were observed between the two groups at the completion of active treatment or on follow up at 52 and 78 weeks. There were no time effects of treatment on scores. Contrary to expectation, baseline and average QOL did not predict retention in treatment.

Conclusion: In contrast to prior research, our findings did not demonstrate significant changes (improvements or decreases) in QOL associated with XR-NTX treatment. Clinicians may consider

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that individuals receiving XR-NTX may not experience changes in perceived well-being in response to treatment and consider discussing with patients that they may not necessarily perceive improvement in their QOL. This may help to ground patient's expectations about the effects of treatment and potentially reduce attrition from treatment with opioid antagonists.

Keywords

Opioid use disorder; medication for opioid use disorder; quality of life; extended release naltrexone; criminal justice; medication assisted treatment

1. Introduction

Opioid overdose is a leading cause of death in individuals involved with the legal system.[1–3] Yet, individuals with legal involvement often encounter barriers to initiation and maintenance of treatment with Medications for Opioid Use Disorders (MOUD), the "gold standard" treatment for opioid use disorders, which include both opioid agonist and opioid antagonist treatments.[4,5] In particular, many criminal justice agencies are unwilling or reluctant to provide opioid agonist medications (i.e., methadone and/or buprenorphine),[6–8] despite their well established effectiveness in managing opioid use disorders because of limited understanding about the need for such medications, concerns about diversion, and potential for abuse. In recent years, however, there has been slow but notable increase in acceptance of all types of MOUDs in legal settings, but especially for opioid antagonists (i.e., extended release naltrexone) as these medications cannot be abused.[9–11] When opioid antagonist treatment is provided to individuals during or soon after release from incarceration, few remain in treatment long-term.[12,13] Understanding the impact of opioid antagonist treatment on one's quality of life may help to explain why few individuals with legal involvement remain in medication treatment.

Health-related quality of life (QOL) is a self-perceived measure of physical and mental health wellbeing and their effects on daily functioning.[14] It is also a critically important and empirically supported predictor of retention in treatment across a wide range of medical conditions.[15–18] Individuals whose medical or psychiatric symptoms decrease, but whose perceived sense of wellbeing remains low or unchanged, may not believe their treatment is effective or satisfactory and therefore discontinue. Conversely, improved perception of wellbeing reinforces ones desire to remain in and comply with treatment. While the National Institute of Drug Abuse[19] and addictions researchers[20–23] have long emphasized the importance of measuring QOL as an outcome in substance use disorders research, few studies have directly examined the relationship between medication treatment and changes in QOL.

Limited available research suggests that opioid use disorder (OUD) is associated with significant decreases in one's QOL,[24] such that individuals with OUD have lower QOL than healthy controls, and in some studies, even lower than individuals with serious mental illness.[25] Predictably, treatment with opioid agonist medications, such as methadone and buprenorphine, has been shown to improve QOL.[25–29] However, the impact of opioid agonist treatments on QOL may differ by medication type. For instance, those receiving

methadone maintenance treatment reportedly showed an earlier improvement (within the first month) in QOL than those on burprenorphine (who experienced improvements within 4 months).[30] Others have found that improvements to QOL on buprenorphine can be seen at 3 months, still below what is generally observed in those receiving methadone.[28,29] Research on individuals in opioid agonist treatment has identified several distinct trajectories on their QOL. For instance, some individuals experienced no change in their QOL, regardless of whether at baseline they had low or high QOL and then received opioid agonist treatment for one year. The majority, however (55%), reported significant and meaningful improvements (overall mean increase of 23.9%) from baseline to end of treatment.[31] These findings suggest that there might be some individual, thought not well understood, factors that impact overall response to medication treatment on QOL, as well as differences by medication type.

Research on the impact of opioid antagonist treatments (e.g., extended-release naltrexone; XR-NTX) on QOL is even more limited than with opioid agonists, with few studies showing overall improvement in QOL. Instead, existing research suggests that some features of QOL improve while others remain unchanged. One study found that baseline QOL scores moderated the effectiveness of XR-NTX treatment response only for individuals receiving XR-NTX who did not have limitations in mobility (a subscale of QOL).[32] Another study using a small sample ($n = 38$) of healthcare professionals with opioid use disorder found a significant improvement on mental health component but not physical health component scores of QOL at 24 months.[33] An open-label, single-arm, multi site study of community dwelling adults found that the physical health component of QOL and health status improved at 6 months of treatment with XR-NTX.[34]

More broadly, QOL during addictions treatment has been shown to predict sustained remission[18,35] and self-perceived recovery from drug use.[36] However, no known studies have examined whether QOL at baseline and/or during treatment predicted retention in treatment with XR-NTX, an important question given increased acceptance of this medication in legal settings.

The current study seeks to examine the impact of XR-NTX on QOL in a randomized controlled, multi-site trial of individuals involved in the legal system. Specifically, we sought to examine whether (1) significant difference in QOL exist between individuals who received XR-NTX as compared to Treatment As Usual (TAU) at the end of treatment (at 27 weeks) and on follow up (at 52 and 72 weeks), and (2) whether QOL predicted retention in XR-NTX treatment.

2.   Methods

2.1.   Participants

The participants were 308 community-dwelling adults with opioid dependence based on criteria from the Diagnostic and Statsistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR),[37] which was the most recent version of the DSM in use at the start of study recruitment. All participants were between the ages of 18 and 60, willing to participate in opioid-free treatment maintenance, had negative urine toxicology screens for all opioids prior to randomization, and were (1) currently supervised by parole or probation

(74%), (2) receiving other type of criminal justice supervision (e.g., drug court; 5%), or (3) had been released from jail or prison in the past year (21%). Individuals with co-occuring alcohol dependence (using DSM-IV-TR criteria) were excluded. Participants were recruited from medical clinics and outpatient and inpatient addiction treatment program, through advertisemens in print, on the radio, and online. See Lee and colleagues for additional study information.[38]

2.1.   Study methods

Study participant were recruited at five sites around the US and were randomized to either receive XR-NTX or treatment as usual (TAU), which included psychosocial interventions and/or attendance at mutual peer support groups. The experimental group received 380 mg of XR-NTX, administered by study clinicians, every 4 weeks for a total of six injections. Both groups received counseling about ways to reduce risk of relapse and overdose and were provided with the same resources for community-based treatments. Participants were not provided with Naloxone but may have had access to it in the community.

The active phase of the study lasted 6 months, after which XR-NTX was discountinued. There were three follow up evaluations for all study participants at 27 (upon completion of active phase), 52, and 78 weeks. Study participants completed self-report measures and questionnaires at baseline and every 4 weeks subsequently for a total of 10 study assessments.

We obtained approval from the University of Massachusetts Medical School IRB to conduct secondary data analysis of an existing and completed data source. We did not have access to any identifying information about the study participants. The original study received IRB approval from each of the five sites conducting the study and obtained written informed consent from all study participants.

2.2.   Study variables and analysis

Health related quality of life was measured using Euro QOL 5 dimensions (EQ-5D).[39] The EQ-5D has been validated for use in research and clinical settings for patients with opioid use disorders.[21,40] The EQ-5D has five individual items (i.e., components), which assess impairments to mobility, self-care, usual activities (e.g., work, family or leisure), and presence of pain/discomfort and anxiety/depression. Each item has three levels of response (none, some, or extreme), with low scores indicative of better functioning (i.e., absence of a problem). Additionally, there is a visual analogue scale of participant's health state today (day of the evaluation), ranging from 0 (worst imaginable state) to 100 (best imaginable state). We analyzed QOL in three ways, using (1) individual items (5 scores), (2) summary index (weighted value from 0 to 1, with higher values indicating better health), and (3) health state today score (0–100).

Attrition from the study was defined as missing a monthly injection or declining to receive the injection. After randomization, 7 of the participants (5%) declined to receive any injections. For the first injection, 146 (95%) participants received XR-NTX, for the second injection −132 (86%), third −119 (78%), fourth −111 (73%), and fifth −100 (65%), and sixth and final −93 (61%). Participants were still eligible to remain in the study and

continue completing self-report questionnaires even if they were no longer actively receiving XR-NTX.

2.3.   Statisical analysis

Descriptive statistics are summarized by randomized outcomes, with mean and standard deviation reported for continuous variables and frequency and its percentile for categorical variables. Kolmogorov-Smirnov test was performed to compare the distribution of each QoL components, summary index, and health state today score between the two groups at each week. To compare the change from baseline, t-test was performed for week 27, 52, and also 78. To account for intercorrelation of within subject responding and non-normal distribution, Generalized estimating equation (GEE) was used to assess for change in QoL scores (total score, health state today and components) by time within group. The probability of a type I error was set at 0.05, and all testing was two-sided. All analyses were performed using SAS® 9.4 software.

3.   Results

Only individuals who completed two or more QOL assessments were included, resulting in a sample of 297 (TAU = 148, XR-NTX = 149). The participants were predominantly male, of ethnic minority, and were currently on supervision (i.e., probation or parole; see Table 1 for summary). There were no significant differences in summary index score, health state today, or individual item rating between XR-NTX and TAU groups at baseline. During the study, some individuals in TAU and NTX groups reported receiving opioid agaonist treatment (i.e., methadone or buprenorphine). Specifically, $n = 38$ individuals in TAU and $n = 25$ individuals in XR-NTX group reported receiving opioid agonist treatment and had positive urine tests for either methadone or buprenorphine at that time. We conducted post-hoc analyses (reported below) by removing these individuals from their respective groups, but overall found no differences in our findings.

3.1.   Qol change in response to treatment

Contrary to our hypothesis that QOL would improve with treatment, there were no significant difference between the two groups at each of the three time points: week 27 (end of active treatment) (p-value = .998 and .372 for summary index score and health state today respectively), week 52 (p-value = .998 and .154 for summary index score and health state today respectively), or week 78 (p-value =.349 and .871 for summary score and health state today respectively) (Table 2). We conducted post-hoc analyses to determine if there were any other times when there were significant differences between groups when QOL was measured (weeks 5, 9, 13, 17, 21, or 25). We found only one significant difference between groups at week 5 (uncorrected p-value =.012), with XR-NTX group having higher scores than TAU group on the health state today score only, but we believe these findings are not clinically significant.

We also investigated time effects of QOL using GEE in the XR-NTX and TAU groups during active treatment (up to week 27). Overall QOL as measured by the index score did not change over time in either the XR-NTX (p-value = 0.251) or TAU group (p value = .947;

see Table 3). Compared to baseline, treatment using XR-NTX did not improve QOL for summary index score (−0.034 [−0.007–0.074]) or health state today (2.12[−1.745–5.983]). The only significant time effect was in the XR-NTX group for mobility (p = .032) and pain and discomfort scores (p-value = .042).

We conducted post hoc analyses by removing any individuals, in either TAU or XR-NTX groups, who received opioid agonist treatment during study enrollment to assure that our findings were not skewed by changes in QOL associated with receipt of opioid agonist medication. For all individuals who did not receive opioid agonists, there were no significant difference between two groups at any of the three time point using Kolmogorov-Smirnov tests (P values for summary index scores and health state today at week 27: 0.796 and 0.314, week 52: 0.892 and 0.238, week 78: 0.303 and 0.830). We also investigated if there was time trend using GEE. Overall QOL summary index score did not change over time in either XR-NTX (p-value = 0.120) or the TAU group (p-value = 0.505). Compared to baseline, receiving XR-NTX did not improve QOL as measured by the summary index score (−0.034[−0.007–0.074]) or health state today (3.26[−1.513–8.026]) at week 27. The only significant time effect was in the XR-NTX group for pain and discomfort scores (p-value=.045).

3.2.   Retention in NTX treatment

We further examined whether baseline QOL, as measured by total QOL and health state today, predicted retention in treatment for the XR-NTX group at completion of study: it did not based on summary index score (OR[CI] = 0.732[0.73–7.34], p = .791) and health state today (OR[CI] = 1.001[0.982–1.020], p = .943). We subsequently examined whether average QOL scores predicted retention using logistic regression. The average summary index score was not predictive of treatment retention (p = .636), and while health state today was significant (p = .036), it was not necessarily predictive as odds ratio hovered around 1 OR[CI] = 0.988[0.976–0.999].

We conducted post hoc analyses by removing any individuals who reported receiving opioid agonist treatment. The baseline QOL did not predict retention in treatment in the XR-NTX group at the completion of study as measured by the summary index score (OR[CI] = 0.495 [0.056–4.401], p = .528) or by the health state today OR[CI] = 1.000 [0.982–1.019], p = .988). We also examined if the average QOL scores predicted retention, but it did not as measured by summary index score (OR[CI] = 1.351 [0.391–4.665], p = .635 or health state today OR[CI] = 1.001 [0.982–1.020], p = .943).

4.   Discussion

This study contributes to a growing literature about the impact of MOUDs, specifically XR-NTX on QOL, for individuals with criminal justice involvement and subsequently at high risk for death from overdose. In contrast to prior research on methadone,[27,28] buprenorphine,[26,29,30] and limited data on XR-NTX,[33,34] our findings generally did not demonstrate any significant changes (improvements or worsening) in overall QOL, as measured by the summary index or health state today, associated with treatment with XR-NTX as compared to TAU. This lack of significant change remained even when we

conducted post hoc analyses to remove any participants who reported receiving opioid agonist treatment at any point during the study.

Several possibilities may explain why XR-NTX did not influence broad measures of QOL as measured by the summary index scores or health score today. First, XR-NTX is an opioid antagonist, as compared to other MOUDs which are opioid agonists, and as such it does not activate mu opioid receptors that can normalize feelings of well-being. Indeed, blockade of opioid receptors might reduce the subjective experience of well-being associated with endogenous opioids as well. Second, individuals receiving XR-NTX may have experienced side effects, in the absence of any increased opioid agonist associated changes, which then overall lowered QOL. Lee and colleagues noted that individuals receiving XR-NTX in this sample were more likely to experience adverse effects ($p < .001$) than the control group, including having injection site reaction ($n = 46$, 30.1%), headaches ($n = 29$, 19.0%), and gastrointestinal upset ($n = 28$, 18.3%)[38] However, participants in the TAU group, also reported a range of symptoms, including depression, chest pains, and chronic obstructive pulmonary disease symptoms. Third, individuals who participated in this study required a brief period of abstinence from all opioids. As such, those who are able to abstain long enough to remain opioid abstinent may generally have had higher QOL than individuals who cannot abstain. Finally, our sample differed from the earlier open enrollment, single arm XR-NTX studies.[33,34] Individuals interested in participating and enrolling in XR-NTX research, where they are guaranteed to receive treatment, may differ from those willing to enroll in trials where they may be randomized to TAU.

Looking at the individual QOL scores, there was significant improvement (i.e., reduction in symptoms) on item measuring experience of pain and discomfort. This finding held when we removed individuals who received any OAT during during active phase of the study. No definitive explanation for this can be offered, in speculating it is possible that this finding represents a reduction in opioid-induced hyperalgesia.[41] Some research has also found that use of low-dose naltrexone has produced pain relief in inflammatory chronic conditions (e.g., fatigue syndrome,[42] Chrohn's disease,[43] fibromyolagia,[44] and multiple sclerosis).[45] An alternative explanation is that this is a spurious finding that is statistically but not clinically meaningful.

Contrary to our hypotheses, we found that no QOL measure, including summary index, individual items, or health state today, either at baseline or on average during active treatment predicted retention in the treatment group. Of note, while health state today did initially predict retention, when we removed individuals who received treatment with methadone or buprenorphine, it was no longer significant. This finding counters other findings for an array of other medical and addictions treatments, which have found that QOL is a predictor of treatment retention. This may be due in part to a finding that there is generally no broad improvements in well being associated with XR-NTX treatment. Therefore, individuals may have believed that the treatment they were receiving was not necessarily associated with their recovery, which has clear implications for retention in treatment addressed below.

This research has several limitations. First, all of the participants in this sample had legal involvement and may not be representative of individuals in the community with regard to their perceived QOL and associated health functioning. Second, these participants may have been limited by access to other treatments, given that at the time of this research, most criminal justice agencies, if not all, were unwilling to allow individuals under their supervision to receive opioid antagonist treatments. As such, this may not mirror experiences of individuals who are able to select which type of medication – opioid agonist or antagonist – they would prefer. Third, we examined only health-related QOL, and it is possible that participants did experience improvements in other aspects of QOL, including social and occupational. Fourth, it is possible that due to study requirements of abstinence from opioid use for enrollment in the study, participants may have reached their baseline quality of life (i.e., there was a ceiling effect) and therefore few changes were observed during study participation. Lastly, our study examined the impact of QOL for treatment of opioid use disorder. Since XR-NTX is also FDA approved for use with alcohol use disorder, there may be differential QOL effects for treatment of different substance use disorders.

Nevertheless, this research brings forth important findings regarding how XR-NTX impacts QOL and retention in treatment. QOL is a well-documented predictor of retention in treatment for various medical conditions,[16–18] such that those with better QOL are more likely to remain in treatment than those with lower QOL. Yet, in this study, QOL did not predict retention in the XR-NTX group, nor did QOL improve with treatment. This is counter to prior research with opioid agonist treatments, which showed improvements in QOL, and is generally associated with longer retention rates. This is especially concerning for individuals with legal involvement who may be more likely to receive antagonist treatment than opioid agonists. More over, individuals who do enroll in antagonist treatment may expect to experience subjective improvements in their well being, but given our findings in a randomized controlled trial, using multiple indicators of QOL, may not.

These findings have important implications. While additional research is needed to corroborate our findings, clinicians should consider that individuals receiving XR-NTX may not experience subjective experiences of well-being (i.e., improvements in QOL) in response to receipt of treatment. One possible way to address this is to provide additional psychoeducation around expectation of treatment, specifically that patients may not necessarily experience improved sense of wellness. This may help to ground patients' expectations and potentially reduce attrition from treatment. Additionally, future research should examine ways of improving QOL, given its relationship to retention in treatment.

Acknowledgements

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Table 1.

Baseline characteristics of the participants.

Variables	NTX (N= 149)	TAU (N= 148)
Age (mean ± sd)	44.5 ± 9.3	43.5 ± 9.2
Years education (mean ± sd)	11.5 ± 2.2	11.5 ± 1.8
Male (n, %)	126 (84)	126 (85)
Race (n, %)	31 (20.8)	28 (18.9)
White		
Black	80 (53.7)	73 (49.3)
Other	2 (1.3)	3 (2.03)
Hispanic	35 (23.5)	43 (29.1)
Missing	1 (0.7)	1 (0.7)
Heroin use in past 30 days (n, %)	31 (20.8)	40 (27.0)
Health Insurance	105 (70.5)	106 (71.6)
Any		
Medicaid	66 (44.3)	62 (41.9)
Currently employment (n, %)	26 (17.5)	29 (19.6)
Currently serving an adjudicated sentence that includes community supervision (n, %)	117 (78.5)	117 (79.1)
Status with respect to supervision by criminal justice system (n, %)	54 (36.2)	50 (33.8)
Parole		
Probation	55 (36.9)	60 (40.5)
Other	8 (5.8)	7 (4.7)
Missing	32 (21.5)	31 (21.0)

Table 2.

Mean (SD[†]) of QOL scores at week 27, 52 and 78.

Time	Randomized outcome	Mobility [0–2][*]	Self-care [0–2][*]	Usual activities [0–2][*]	Pain or discomfort [0–2][*]	Anxiety or depression [0–2][*]	Health State today [0–100][*]	Summary index [0–1][*]
Baseline	TAU	0.21 (0.41)	0.05 (0.23)	0.21 (0.44)	0.50 (0.58)	0.55 (0.57)	80.10 (20.24)	0.84 (0.16)
	NTX	0.25 (0.45)	0.03 (0.16)	0.17 (0.40)	0.57 (0.61)	0.50 (0.58)	81.19 (20.37)	0.83 (0.17)
Week 27	TAU	0.24 (0.43)	0.09 (0.29)	0.26 (0.46)	0.54 (0.65)	0.43 (0.63)	79.80 (20.86)	0.83 (0.21)
	NTX	0.26 (0.44)	0.06 (0.24)	0.18 (0.39)	0.48 (0.61)	0.42 (0.59)	82.79 (17.98)	0.85 (0.18)
Week 52	TAU	0.18 (0.41)	0.04 (0.20)	0.19 (0.39)	0.55 (0.65)	0.44 (0.63)	81.15 (17.38)	0.83 (0.20)
	NTX	0.29 (0.47)	0.04 (0.19)	0.22 (0.46)	0.52 (0.64)	0.50 (0.65)	82.17 (18.96)	0.82 (0.20)
Week 78	TAU	0.21 (0.43)	0.05 (0.21)	0.20 (0.40)	0.55 (0.63)	0.43 (0.60)	80.36 (17.47)	0.84 (0.18)
	NTX	0.30 (0.48)	0.07 (0.29)	0.23 (0.44)	0.63 (0.67)	0.56 (0.66)	80.67 (18.73)	0.80 (0.21)

[†] Standard Deviation.

[*] Possible range of score.

Table 3.

GEE findings of significance in QOL scores by group (Type 3 Wald statistic *p*-values).

QoL scores	Group	
	NTX	**TAU**
Index summary score	0.251	0.947
Mobility	0.302	0.693
Self-care	0.381	0.208
Usual activities	0.485	0.001
Pain or discomfort	0.045	0.679
Anxiety or depression	0.131	0.143
Health State today	0.586	0.271