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Long-term follow up study of community based patients receiving XR-NTX for Opioid Use Disorders

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Abstract

Background and Objectives—Extended-release naltrexone (XR-NTX) is FDA-approved to prevent relapse in patients with Opioid Use Disorder. However little is known about long-term use among community-based outpatients.

Methods—Retrospective chart review and long-term follow-up survey among individuals (N=168) who entered an outpatient XR-NTX trial between 2011–2015, during which participants were offered 3 monthly injections of XR-NTX at no cost. The survey consisted of 35 questions covering a total of 4 domains: (1) Substance use; (2) Treatment continuation; (3) Barriers; and (4) Attitudes.

Results—57 respondents were successfully surveyed, including 50% of those initially receiving all 3 XR-NTX injections ("study completers") in the parent study. Study completion was associated with superior outcomes and less likely relapse (defined as daily use), with a much greater time to relapse despite higher rates of concurrent non-opioid substance use. However the majority of participants discontinued treatment with XR-NTX at study completion, largely due to attitudes of "feeling cured" and "wanting to do it on my own" rather than external barriers such as cost or side effects.

Conclusion—Patients who initiate treatment with XR-NTX might benefit from anticipatory guidance and motivational techniques to encourage long-term adherence as many will experience internal barriers to continuation. Our findings are reassuring that few patients experience side effects or adverse events complicating the effectiveness or safety of long-term use of XR-NTX.

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Contributors

ARW conceived the study design. ARW, VB, and KM wrote the protocol and collected data. ARW wrote the first draft of the manuscript including the statistical analyses and results sections. All authors contributed to the interpretation of the results and revising the paper. All authors read and approved the final submission.

Disclosures

All remaining authors report no financial relationships with commercial interests.

Scientific Significance—Among outpatients who successfully receive 3 monthly XR-NTX injections, many will prematurely discontinue treatment due to internal attitudes, such as “feeling cured.”

Keywords

Opioid use disorders; XR-NTX; medication assisted treatment; long-term outcomes

Introduction

The opioid epidemic now encompasses more than 2.4 million individuals with opioid use disorders (OUD), and over 29,000 opioid-related overdose deaths a year (1). Currently three medication-assisted treatment (MAT) modalities are FDA-approved for treating patients with OUD: methadone, buprenorphine, and naltrexone in both pill form and an extended release monthly injection (XR-NTX) (2,3). XR-NTX was most recently FDA-approved in 2010. It has faced considerable resistance to widespread use due to access barriers such as a lack of trained providers, financial and insurance restrictions (cost), and theoretical concerns about side effects (such as anhedonia) and overdose risk with treatment discontinuation (4,5). However studies of XR-NTX have consistently shown substantially reduced rates of both opioid use and overdose death compared to treatment as usual (6,7), it is well-tolerated (8), and it is associated with a reduction in depressive symptoms (9).

To date, no published study has specifically assessed reasons for discontinuation among community-based outpatients with OUD receiving XR-NTX. The few long-term studies (>6 months) that have been published have all provided XR-NTX as study drug, limiting generalizability to patient populations outside of clinical research settings. Prior studies do offer insight into concerns about tolerability (8), effectiveness (6,7), and adherence (10) in the community. A multisite feasibility study for the use of XR-NTX documented only 2 serious adverse events among 233 monthly injections (10). A more recent multisite open label randomized trial (6) among offenders with OUDs (N=308) found 7 overdoses (fatal and non-fatal), all among the arm randomized to treatment without XR-NTX. Finally, an unrelated continuation study for patients *with alcohol use disorders* in primary care settings (11) specifically investigated reasons participants ended treatment prematurely and identified several recurring responses including, “wanting to do it myself” [without medication], being “tired of the shot,” and an attitude of having achieved success and not needing additional care. Of note, side effects were not reported as reasons for discontinuation among these study extenders.

In summary, studies demonstrate the feasibility of long-term use (up to 15–41 injections) of XR-NTX (8,10,11), but provide limited insight into barriers- both internal and external- that community-based outpatients with OUD may experience when attempting to continue XR-NTX therapy in real-world settings. Of concern, even in these studies in which XR-NTX was provided as a free study drug, rates of continuous adherence struggled to surpass 40–60%, reflecting the challenge of treatment retention common among patients with OUD. Regarding adverse events, these studies do not provide evidence of additional risk of overdose among patients with OUDs who receive XR-NTX.

In order to specifically investigate the long-term treatment effects of XR-NTX therapy on patterns of substance use, long-term trends in treatment adherence, and adverse events among community-based patients in the outpatient setting, we conducted a retrospective survey of former study participants who had entered an open-label XR-NTX study between July 2011–July 2015 in New York City and were referred out to community providers (12). Emphasis was placed on identifying internal and external barriers to treatment continuation with XR-NTX, spanning internal belief systems, social networks, insurance obstacles, intervening life stressors, and limited access issues (i.e. lack of experienced providers).

Methods

Participants were initially randomized in an outpatient, open-label, parallel-group, clinical trial that began recruitment summer of 2011 (12). Participants were treatment-seeking individuals (age 18–60) with an active ICD-9 diagnosis of opioid dependence or ICD-10 diagnosis of OUD. The trial occurred at the New York State Psychiatric Institute (NYSPI), a research clinic in an academic medical center, in New York City.

The initial study was designed to assess successful XR-NTX induction rates according to outpatient detoxification protocols with varying combinations of buprenorphine and low-dose oral naltrexone (13–15). During the induction phase participants were seen daily by a therapist for psycho-education and counseling. During the first 5 weeks following the first XR-NTX injection, participants received therapy informed by cognitive behavioral and relapse prevention strategies twice per week, and then weekly for the remaining period. Participation in mutual-help groups (such as AA/NA) was only discussed when patients brought it up or in cases where additional peer-support was determined to be necessary. Initially, participants who successfully received their first XR-NTX injection continued with outpatient treatment for 4 weeks. Those who were retained at Week 5 were offered up to 2 additional XR-NTX injections (for a total of 3 injections) for an active treatment period of up to 12 weeks. Subsequently, participants were offered referrals to continue XR-NTX treatment at suitable community programs and in accordance with their wishes. No follow up assessments were built into the original protocol beyond week 14.

IRB approval was obtained from the New York State Psychiatric Institute IRB as an amendment to the original study. Participants who entered the original induction study before July 1, 2015 (N=168) were deemed eligible to be surveyed as they would have a minimum of 6 months since enrollment before survey contact. Participants were recruited for the retrospective survey through phone contact (phone calls and texts) and mailed letters. If former participants contacted staff on their own accord they were also invited to be surveyed. After 5 unsuccessful attempts, potential participants were deemed unreachable.

The survey was designed by study investigators and consisted of 35 questions covering a total of 4 domains: (1) Substance use; (2) Treatment continuation following study participation (any treatment received following week 14); (3) Barriers (internal and external) to continuing XR-NTX treatment, including adverse events; and (4) Attitudes toward recovery, medication assisted treatment, and experiences specifically with XR-NTX. Participants were remunerated with a $25 cash gift card for completing the survey (typically

over a 15–20 minute phone call) and offered an additional $25 for providing an on-site confirmatory urine specimen which was tested for opioids (morphine, oxycodone, methadone, buprenorphine), psychostimulants, and benzodiazepines.

Descriptive statistical analyses were performed to assess for differences between 3 groups. Bivariate analysis using t-tests for continuous variables and Chi-square tests for binary variables were performed to detect p values <0.05. The primary group of interest was composed of participants who successfully received all 3 injections in the original parent study ("study completers," N=54) and who were referred out to continue XR-NTX treatment in the community after 12–14 weeks of active treatment during study involvement. Additionally, we attempted to reach participants (N=34) who only received 1–2 injections (and were not referred out due to early study discontinuation) and the group who entered the parent study but failed outpatient detoxification (N=80) and never successfully received XR-NTX (i.e. received 0 injections) for comparison [such patients were referred out for community based treatment unless they were lost to follow up].

Results

Fifty-seven unique respondents were successfully surveyed and included in our final analysis. Respondent characteristics are tabulated in Table 1 by category of initial XR-NTX induction (received all 3 injections, only 1–2 injections, or unsuccessful induction with 0 injections). Response was most limited by difficulty in successfully reaching participants with outdated contact information, some of whom had enrolled in the parent study more than 36 months before survey inception. Only 1 former participant was reached who refused to participate. Otherwise, all successfully reached former participants completed the survey. The average follow up time interval between initial study completion and survey response was approximately 21 months.

Our main population of interest was the group that received all 3 injections ("study completers") and was referred out to continue treatment. Among these 54 individuals, 27 (50%) completed the follow up survey. Additionally, 11 of 34 (32.4%) participants who received 1–2 injections completed, as did 19 of 80 (23.8%) participants who never received an injection and were lost to follow up within the first week of parent study enrollment.

Substance use

Rates of using opioids at least once since study completion were comparable across populations. Although respondents who had received all 3 injections and were referred out to continue XR-NTX reported slightly lower rates of any opioid use following study completion (19 of 27 (70.4%) versus 9 of 11 (81.8%) of those receiving 1–2 injections and 16 of 19 (84.2%)) of those receiving 0 injections (See Table 2), this finding did not reach significance. Study completers were significantly less likely to report ever progressing to daily opioid use (11 of 27 (40.7%)) compared to those receiving 1–2 injections or 0 injections (7 of 11 (63.6%) and 16 of 19 (84.2%))(p=0.012). Additionally, the average time to progress from any opioid use to daily use was longer for respondents in the group receiving all 3 injections (68.8 days) compared to those only receiving 1 or 2 injections (12.4 days) or 0 injections (5.5 days)(p<0.001).

Regarding active (past month) substance use, there was no significant difference in the rate of opioid abstinence between respondents by group (range of 29.6%–36.4%). Of note, 15 respondents provided in-office urine samples for drug testing, all of which were concordant with self-report of recent opioid use or abstinence. There was not a significant relationship between likelihood of reporting any past month opioid use and the likelihood of having ever progressed to daily use since parent study completion, however our study may have been under powered to detect such a difference. There were significant differences in patterns of non-opioid drug use (See Table 2) as respondents who had received at least 1 injection were consistently more likely to report active substance use (including alcohol and tobacco) such as marijuana than those not receiving any injections.

Treatment continuation

Overall, 31 respondents (54.4%) were not in active treatment (had not received any substance abuse treatment in the month of their survey completion). Respondents who received all 3 injections and referrals to continue XR-NTX were actually less likely to report current (past month) substance abuse treatment (7 of 27 (25.9%)) than those receiving only 1–2 injections (5 of 11 (45.5%)) or 0 injections (8 of 19 (42.1%)) (p=0.031). Further, of all respondents, 20 (35.1%) reported never receiving treatment of any kind since leaving the initial study. Of note, these participants were not statistically more likely to report opioid use (active use or ever use) than those who had received any substance abuse treatment (data not shown). The majority of respondents (42 of 57 (73.7%)) reported never receiving a subsequent XR-NTX injection after leaving the study. Among the 15 participants who did receive a subsequent injection, an average of 6.1 injections were received (range of 1–14). There was a trend in the data suggesting more recent parent study participants (i.e. those who enrolled within just 1–2 years preceding the survey) were more likely to report ever receiving an injection after study completion.

Barriers to continuation including adverse events

Among the population of interest (study completers who received all 3 injections), a variety of reasons for not continuing with XR-NTX injections, spanning internal and external barriers, were endorsed. Most commonly, these respondents who discontinued XR-NTX (N=21) reported internal barriers such as thoughts that they “felt cured,” (11 of 21 (52.4%)) and/or that “I wanted to do it on my own,” (5 of 21 (23.8%)). Those who discontinued XR-NTX after the 3 study injections were also much less likely to report side effects as a cause (1 of 21 (4.8%)), compared to respondents who only received 1 or 2 study injections before discontinuation (6 of 10 (60%))(p=0.002). The most commonly endorsed “side effect” among this latter group was interference with ongoing non-opioid substance use (i.e. alcohol) (3 of 10 (33.3%)), in addition to an injection site reaction (1 of 10 (10%)), and/or other physical complaints (3 of 10 (33.3%)) such as headache or sleep disturbance.

Regarding adverse events, only 3 overdoses have been documented among the 168 initial parent study participants since July 2011. One overdose was fatal and reported to staff prior to the conception of the survey. Within our findings, 2 non-fatal overdoses were reported by respondents (spanning 99.75 total patient-years based on respondent self-report and date of survey), one of which received naloxone reversal. One occurred among study completers

who received 3 injections (1 of 27 (3.7%)) and the other among the group receiving 0 injections (1 of 19 (5.3%)).

Attitudes toward recovery, medication assisted treatment, and experiences with XR-NTX

Regarding social networks, respondents who initially received at least one injection in the parent study were more likely to report knowing someone on XR-NTX in the past year than those who did not receive an injection. Respondents were more likely to report that such contacts had positive experiences on XR-NTX if they had received an injection themselves (75% v 50%, p=0.056) [respondents who reported knowing someone else on XR-NTX were asked if those contact had “positive or negative experiences” as a marker of their global impression toward XR-NTX treatment]. Overall, respondents were twice as likely to report knowing someone in the past year on buprenorphine as XR-NTX. Respondents who reported knowing someone on buprenorphine were much more likely to report that those individuals had mixed or negative treatment experiences (52.9%) than those on XR-NTX (12.5%) (p=0.01). A majority of those receiving at least one initial injection also reported they agreed or strongly agreed that they would recommend XR-NTX to others (33 of 38 (86.8%)).

Discussion

Our findings show that under half of participants who initially received all 3 injections and referrals to continue treatment with XR-NTX in the community successfully received at least one additional injection following study completion. Further, we found that barely a quarter were still receiving XR-NTX during the month of survey response, highlighting challenges to retention in treatment over an extended duration.

Although only a minority of all respondents (20 of 57 (35.1%)) were on a MAT modality at the time of survey response, most denied past month opioid use (39 of 57 (68.4%)). Former participants who were abstinent from opioids at the time of survey contact were arguably more likely to respond to our outreach methods and may be overrepresented in our analysis. Although the majority of respondents were not actively using opioids, many (44 of 57 (77.2%)) had used opioids at least once since leaving the parent study. However there was a substantially lower likelihood and greater time to daily use among patients who received all 3 injections than those who only received 1–2 injections or those who never received an injection, which may reflect patient characteristics at intake as much as benefits of XR-NTX (12,16).

We also identified a consistent theme in that participants who successfully received injections were not only more likely to have used other substances at study entry (12), but also to be active users (i.e. of marijuana, alcohol, and nicotine) at the time of survey response, despite having equivalent rates of past month opioid use as the comparison groups. This finding is consistent with prior studies showing superior outcomes among patients treated for OUD who have concurrent substance use (17) and among those with intermittent marijuana use (18). This may reflect a substitution phenomenon whereby patients use multiple substances as coping mechanisms or that other substances, such as marijuana, may lessen either withdrawal symptoms or the side effects of naltrexone (19).

At the outset of the study there was concern that participants may have run into external barriers (i.e. lack of provider access or insurance reimbursement) complicating their ability to continue with monthly injections. Our results show that the most common reasons participants quit treatment with XR-NTX after 3 injections were internal beliefs such as "feeling cured" or wanting to "do it on my own," consistent with prior research among XR-NTX outpatients with alcohol use disorders (11) and impaired insight common among patients with substance use disorders (20). The high prevalence of such internal barriers to treatment continuation suggests providers might want to incorporate anticipatory guidance and motivational interviewing techniques to help patients initiating XR-NTX remain committed to continuing treatment beyond early periods of abstinence. Paradoxically, high rates of abstinence ensured by a monthly injection with an opioid antagonist may undermine patients' adherence to long-term treatment.

Reassuringly, few overdoses (2 per 99.75 person years) were reported by survey respondents. We found no indication that patients who received XR-NTX had a disproportionately elevated increase in risk of overdose compared to other treatment modalities, irrespective of the number of injections received or whether or not they discontinued treatment. More research is needed into predictive factors of which patients might best respond to XR-NTX and which may be at risk for overdose with treatment discontinuation (21).

Our study was limited by response bias wherein survey respondents may not be fully representative of the parent study participants we were unable to reach as we were only able to contact 33.9% (55/168) of original participants. Foremost, participants may have been less likely to respond if they were experiencing worse outcomes (including overdose and overdose death). Additionally, much of our follow up data was dependent on self-report. However, our methodology and response rate are comparable to prior studies (22). Regardless, there were no incentives for respondents to intentionally misrepresent their condition and urine toxicology (when available) was concordant with self-report. Self-report may have also been affected by recall bias, especially for respondents with more distal enrollment in the parent study. Finally, the initial study population may have limited external generalizability as participants had high rates of employment and other obligations that led them to initially prefer an outpatient detoxification.

Conclusion

Our findings suggest that community-based patients with OUD successfully initiating XR-NTX would benefit from anticipatory guidance and motivational techniques to encourage long-term use as many will experience internal barriers to treatment continuation such as false beliefs that they have been cured or would no longer benefit from XR-NTX. Despite frequent XR-NTX discontinuation, many study completers who responded to the survey had achieved stable cessation of opioid use suggesting this group had protective factors or supports warranting further exploration. Overall, respondents reported few side effects or adverse events (such as overdose) complicating the effectiveness or safety of XR-NTX as a long-term treatment modality. However, attention to side effects bothering early initiates following the first one or two XR-NTX injections may mitigate early treatment

discontinuation. Importantly, while not trivial, only a few patients endorsed external barriers to treatment continuation. Rather, internal belief systems evidenced a disproportionate impact on recovery trajectories beyond the initial 12 weeks of treatment.

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Table 1

Survey Respondent Characteristics by Parent Study XR-NTX Induction Success

	"Study Completers" received all 3 injections (N= 27)	**Received 1–2 injections (N=11)**	**Unsuccessful induction (0 injections) (N= 19)**	**P**
Male	24 (88.9%)	10 (90.9%)	16 (84.2%)	ns
Age, years (SD)	33.4 (13.2)	33.4 (10.1)	39.2 (12.1)	ns
Caucasian	16 (59.3%)	9 (81.8%)	9 (47.4%)	ns
Hispanic	7 (25.9%)	2 (18.2%)	5 (26.3%)	ns
African American	3 (11.1%)	0	3 (15.8%)	ns
Asian	0	0	2 (10.5%)	ns
Native American	0	0	0	ns
Other	1 (3.7%)	0	0	ns
Heroin as primary opioid used	11 (40.7%)	5 (45.5%)	16 (84.2%)	0.01 (1=2<3)
Marijuana use	14 (51.9%)	3 (27.3%)	4 (21.1%)	0.064 (1>3)
Severity of Use				
MEQ*/day mg (SD)	251 (114)	249 (140)	318 (241)	ns
Age of regular use (years, SD)	24.8 (9.9)	27.7 (6.9)	29.1 (9.3)	ns
Years of regular use at enrollment (SD)	8.6 (10.9)	5.6 (4.3)	10.1 (8.5)	ns
Injection as primary route ingestion	2 (7.4%)	2 (18.2%)	9 (47.4%)	0.006 (1=2<3)

*MEQ= morphine equivalent doses

Table 2

Results among survey respondents (N=57)

	1. "Study Completers" received all 3 injections (N= 27)	2. Received 1–2 injections (N=11)	3. Unsuccessful induction (0 injections) (N= 19)	P*
Substance Use				
Any opioid use following parent study	19 (70.4%)	9 (81.8%)	16 (84.2%)	**ns**
Opioid use progressed to daily use	11 (40.7)	7 (63.6%)	16 (84.2%)	**0.012 (1<2=3)**
• Time to daily opioid use (days) among those reporting any daily use since parent study	68.8 (+/− 30.7)	12.4 (+/− 32.4)	5.5 (+/− 10.7)	**<0.001 (1>2=3)**
Any opioid use in past month of survey	8 (29.6%)	4 (36.4%)	6 (31.6%)	**ns**
• Heroin as primary opioid	4 (14.8%)	2 (18.2%)	6 (31.6%)	**ns**
• Injection drug use	0 (0%)	0 (0%)	4 (21%)	**0.018 (3>1=2)**
Past month cocaine use	3 (11.1%)	0 (0%)	0 (0%)	**ns**
Past month marijuana use	7 (25.9%)	6 (54.5%)	2 (10.5%)	**0.031 (2>3)**
Past month alcohol use	15 (55.6%)	4 (36.4%)	4 (21.1%)	**0.033 (1>3)**
Past month nicotine use	16 (59.3%)	6 (54.5%)	5 (26.3%)	**0.038 (1>3)**
Overdose (none were fatal)	1 (4.8%)	0 (0%)	1 (5.3%)	**ns**
Treatment Continuation				
Received XR-NTX after study completion	13 (48.1%)	2 (18.2%)	0 (0%)	**0.001 (1>3)**
• Number of injections received	6.5 (+/−3.7)	3 (+/−2.8)	N/A	**ns**
Active treatment (any, not including AA/NA)	7 (25.9%)	5 (45.5%)	8 (42.1%)	**ns**
• XR-NTX	6 (22.2%)	1 (9.1%)	0 (0%)	**0.002 (1>3)**
• Buprenorphine	0 (0%)	2 (18.2%)	3 (15.8%)	**ns**
• Methadone	1 (3.7%)	1 (9.1%)	5 (26.3%)	**ns**
• Psychotherapy/groups	5 (18.5%)	1 (9.1%)	6 (31.6%)	**ns**
Attitudes				
Know someone on XR-NTX (past year)	11 (40.7%)	1 (9.1%)	6 (31.6%)	**ns**
• Reports positive effect	8 (29.6%)	1 (9.1%)	3 (15.8%)	**ns**
Know someone on buprenorphine (past year)	19 (70.3%)	6 (54.5%)	13 (68.4%)	**ns**
• Reports positive effect	8 (29.6%)	2 (18.2%)	9 (47.4%)	**ns**
Would recommend XR-NTX to others (agree/ strongly agree)	24 (88.9%)	9 (81.2%)	11 (57.9%)	**0.044 (1>3)**
Barriers to continuing XR-NTX (among subgroup no longer receiving XR-NTX)	**N=21**	**N=10**	**N=19**	
Internal				
• "Felt cured"	11 (52.4%)	2 (20%)	N/A	**ns**
• "Wanted to do it on my own"	5 (23.8%)	1 (10%)	N/A	**ns**
Side Effects	1 (4.8%)	6 (60%)	N/A	**0.002 (1<2)**
External				
• Cost	4 (19%)	2 (20%)	N/A	**ns**

	1. "Study Completers" received all 3 injections (N= 27)	**2. Received 1–2 injections (N=11)**	**3. Unsuccessful induction (0 injections) (N= 19)**	**P***
• Lacked insurance reimbursement	3 (14.3%)	0 (0%)	N/A	**ns**