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ORIGINAL RESEARCH ARTICLE

Evaluation of Opioid Overdose Reports in Patients Treated with Extended-Release Naltrexone: Postmarketing Data from 2006 to 2018

Priya Jain[1] · Kimberley McKinnell[1] · Rose Marino[1] · Prashanthi Vunnava[1] · Marie A. Liles-Burden[1] · Avani Desai[1] · Madé Wenten[1] · James Fratantonio[1] · Sarah C. Akerman[1] · Maria A. Sullivan[1,2] · Gary Bloomgren[1]

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Abstract

Introduction After treatment with naltrexone extended-release injectable suspension (XR-NTX), a μ-opioid receptor antagonist, opioid tolerance is reduced from pretreatment baseline. Patients may be vulnerable to opioid overdose if they attempt to override the blockade during treatment, at the end of a dosing interval, after missing a dose, or after discontinuing treatment.
Objective We analyzed postmarketing data to characterize reporting rates of opioid overdose during treatment with and after discontinuation of XR-NTX.
Methods Postmarketing adverse event reports within the XR-NTX safety database, received 2006–2018, for patients treated with XR-NTX for any indication were reviewed for opioid overdose cases. Assessable cases were categorized by timing of the event from the last dose of XR-NTX (latency): ≤28 days (on treatment), 29–56 days, and >56 days from last dose of XR-NTX. Within each latency group, cases were further classified as serious and, of those, cases that had a fatal outcome.
Results During the 12-year period, an estimated 495,602 patients received XR-NTX. Opioid overdose was reported in 161 cases; of these, 66 contained sufficient information to determine latency. Reporting rates of opioid overdose per 10,000 patients treated were similar among latency groups: 0.54 for ≤28 days (0.24 fatal), 0.34 for 29–56 days (0.16 fatal), and 0.44 for >56 days (0.40 fatal) from the last dose of XR-NTX.
Conclusions Over the 12-year period, the reporting rates of opioid overdose were similar during treatment with or after discontinuation of XR-NTX and <10/10,000 patients exposed. Our findings are limited by the nature of spontaneously reported safety data.

1 Introduction

Approximately 2 million adults in the USA were diagnosed with an opioid use disorder (OUD) in 2018 [1], and opioid overdoses associated with hospitalizations in the USA have risen approximately threefold in the last decade, from 59.8 per 100,000 overall hospitalizations in 1998–2000 to 190.7 in 2015–2016 [2]. People with OUD have a tenfold higher mortality risk than the general population, primarily owing to increased rates of accidental or intentional drug overdose [3, 4]. Opioid overdose deaths in the USA have increased rapidly, from 33,091 (10.4 per 100,000 standard population in the USA) in 2015 to 46,802 (14.6 per 100,000) in 2018 [5].

Opioid agonists (methadone [oral; daily]), partial agonists (buprenorphine [sublingual, buccal, subdermal implant, subcutaneous extended release; most commonly daily]), and antagonists (extended-release injectable suspension of naltrexone [XR-NTX]; monthly) are all effective options in decreasing illicit opioid use in patients with OUD and improving outcomes [6–8]. Opioid agonists and partial agonists have been found to reduce mortality [9], and to date no published studies have been powered to detect changes in mortality rates associated with XR-NTX. However, treatment cessation is associated with an

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✉ Gary Bloomgren
Gary.Bloomgren@alkermes.com

[1] Alkermes, Inc., 852 Winter Street, Waltham, MA 02451, USA

[2] Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY, USA

Key Points

Opioid overdose reporting rates during and after naltrexone extended-release injectable suspension (XR-NTX) were similar (<10/10,000 patients exposed).

Half of the assessable fatal opioid overdoses reported occurred >56 days from the last XR-NTX dose.

Limitations of the XR-NTX postmarketing adverse event report data that were used in this analysis include incomplete data and reporting bias.

increased risk of relapse and of overdose events, including death [10, 11]. Treatment with opioid agonists or partial agonists does not abolish physiological opioid dependence; consequently, a measure of tolerance to opioids is preserved, which reduces mortality risk during adherence [12]. In contrast, with antagonist treatment (which requires detoxification before initiation), XR-NTX provides blockade of the opioid receptor and reduces the risk of relapse during treatment, although it carries a risk of overdose should patients attempt to override opioid receptor blockade during treatment, at the end of a dosing interval, or after missing a dose. Abstinence from opioids can reduce opioid tolerance from pretreatment baseline. Discontinuation of any medication for OUD is associated with a heightened vulnerability for returning to opioid use, with its attendant risks, including overdose death [11].

Clinical trials designed to compare opioid overdose rates for different treatments are currently unavailable. However, the rate of opioid overdose after treatment with oral naltrexone has been shown to be higher than the rate after agonist treatment [10, 13]. However, similar findings were not observed with a 6-month implant formulation of naltrexone [14–17], suggesting that the short duration of action and associated poor compliance owing to daily dosing of oral naltrexone may be a barrier to effective treatment [18, 19]. XR-NTX is a μ-opioid receptor antagonist indicated for the prevention of relapse to opioid dependence after opioid detoxification and the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting before initiation of treatment with XR-NTX [20]. XR-NTX blocks the effects of exogenous opioids for approximately 28 days after administration [20, 21]. However, the blockade is surmountable, and this poses a risk to patients if they attempt to override the blockade during XR-NTX treatment. Following XR-NTX treatment, opioid tolerance is reduced from pretreatment baseline, and increased risk of overdose may also occur at the end of a dosing interval, after missing a dose, or after discontinuing XR-NTX treatment [20].

For this case series analysis, we systematically reviewed all adverse event cases of overdose reported to the manufacturer's (Alkermes, Inc.) XR-NTX global safety system (GSS) database between April 2006 and April 2018. Our aim was to estimate postmarketing reporting rates of nonfatal and fatal opioid overdoses during treatment with and after discontinuation of XR-NTX. We also performed a more conservative sensitivity analysis to estimate the postmarketing reporting rates of nonfatal and fatal all-cause overdose reporting rates.

2 Methods

2.1 Source Data

All adverse event cases of overdose reported to the manufacturer's (Alkermes, Inc.) XR-NTX GSS database between 13 April 2006 and 12 April 2018, collected as part of ongoing postmarketing surveillance conducted by Alkermes, Inc. and regardless of indication, were included in this case series analysis. The XR-NTX GSS database includes spontaneous postmarketing and solicited adverse event reporting from sources including patients, healthcare professionals, the US FDA Adverse Event Reporting System (FAERS), and the medical literature. Serious adverse events were classified as defined by the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) [22]: "any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or results in prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect or is a medically important event (ICH E2A and E2D)." In accordance with pharmacovigilance standards [23], several follow-up attempts were made by Alkermes, Inc. to obtain additional details on each case, particularly on any case reporting a serious adverse event, to ensure that collected data were as complete as possible.

2.2 Search Strategy

The following Medical Dictionary for Regulatory Activities (version 20.1) [24] preferred terms were used to search the XR-NTX GSS database for cases containing events of any overdose, irrespective of agent used: overdose, accidental overdose, and intentional overdose.

2.3 Identification of Opioid Overdose

Overdose events, as described by the reporter, were reviewed to identify events of opioid overdose, either by mention of a specific opioid (prescription or non-prescription) or by mention of a general term (e.g., opioid overdose, overdose of an unspecified opioid). Overdose events that provided no details to verify an opioid overdose (e.g., overdosed, suspected overdose, drug overdose) were not included in the primary analysis (opioid overdose) but were included in the sensitivity analysis (all-cause overdose) described in Sect. 2.7.

2.4 Narrative Review and Latency Adjudication

The narratives of all cases reporting an overdose event were reviewed by a primary reviewer (Alkermes, Inc. employee and author); the reviewer determined whether sufficient information was available to calculate or estimate the time between the last XR-NTX dose and the onset of the overdose event (i.e., event latency). Cases were classified as assessable for the reporting rate analysis if the narrative provided sufficient information to calculate or estimate event latency; this information included either (1) complete dates recorded for the last received dose of XR-NTX and the event onset or (2) adequate information to estimate event latency. Cases were classified as unassessable for the reporting rate analysis if the narrative provided insufficient information on date of XR-NTX dosing or date of overdose event to calculate or estimate event latency. Examples of insufficient information in the narrative (and determined as unassessable for these analyses) may be "The patient initiated XR-NTX on [an unspecified date] and experienced an overdose on January 01, 20XX" or "The patient initiated XR-NTX on January 01, 20XX and experienced an overdose 2 or 3 years later."

Assessable cases were then assigned to an event latency group based on time from the last dose of XR-NTX: ≤28 days (on treatment), 29–56 days, and >56 days from the last dose of XR-NTX. Event latency was calculated as the difference in days between the date of the last XR-NTX treatment and the date of onset of the overdose event. A set of standard criteria was used to minimize variability among reviewers: (1) date of last dose was defined as the dose date reported as "most recent," "last dose," "discontinued" (unless noted that this was not the last date), or "withdrawn"; (2) the initiation dose could be considered the last dose date if the event onset occurred within 28 days of the initiation dose or if the narrative stated that there was only one dose; (3) when no date was provided, latency could be calculated if details such as "x days after last dose" were provided; (4) for cases that provided only month and year, the 15th of the month was assumed for consistency of case adjudication; cases that provided only year of occurrence were considered unassessable; and (5) general time measurements were converted into time in days (e.g., a week was considered 7 days and a month was considered 28 days).

All cases received a secondary review by a physician (Alkermes, Inc. employee and author), who examined the case details and agreed with the latency grouping assignment or flagged the case for discussion and consensus. Cases in which a consensus could not be reached were adjudicated by an additional physician reviewer (Alkermes, Inc. employee and author).

2.5 Exposure to XR-NTX

The number of patients exposed to XR-NTX was estimated based on the cumulative number of XR-NTX units distributed from April 2006 to April 2018 (1,734,607 units) and average number of units used per patient (i.e., persistence factor). The persistence factor (3.5 units/patient) is based on an estimate aligning with the injections per patient from an outcomes registry (median three injections per patient; mean five injections per patient) [25] compared with a more recent commercial claims database analysis demonstrating a median of 9 months of treatment [26]. The proportion of patients receiving XR-NTX for opioid dependence was estimated as 50% of the overall patient exposure, based on the subset of prescriptions for which Alkermes was informed of the indication (data on file). Therefore, from April 2006 to April 2018, an estimated 495,602 patients overall were exposed to XR-NTX (1,734,607 units shipped/3.5 units/patient), regardless of indication, with 247,801 patients exposed to XR-NTX for the indication of opioid dependence; the remaining 247,801 patients were exposed to XR-NTX for alcohol dependence.

2.6 Reporting Rate Calculation

Reporting rates are used to describe the rate at which an adverse event occurs relative to the population exposed. In our analysis, reporting rates were calculated based on the number of opioid overdose events in each latency group relative to the estimated overall patient exposure and expressed per 10,000 patients exposed.

$$\text{reporting rate, opioid overdose} = \frac{\text{opioid overdose events}}{\underset{(n = 495{,}602)}{\textit{estimated overall patient exposure}}} \times 10{,}000 \text{ patients}$$

The 95% confidence intervals (CIs) were calculated using the Clopper–Pearson method [27].

2.7 Sensitivity Analysis

A sensitivity analysis was performed to assess whether use of a broader definition for overdose events would affect the conclusions of the primary analysis. In this sensitivity analysis, any adverse event reported as an overdose was considered (i.e., all-cause overdose) for each latency group. In this analysis, reporting rates were calculated based on the number of all-cause overdose events (irrespective of agent used; opioid, non-opioid, not specified) in each latency group relative to the estimated overall patient exposure and expressed per 10,000 patients exposed. Patient exposure was adjusted to the estimated population of patients who received XR-NTX for the treatment of OUD.

$$\text{reporting rate, all-cause overdose} = \frac{\text{all-cause overdose events}}{\underset{(n = 247,801)}{\textit{estimated overall patient exposure for OUD}}} \times 10{,}000 \text{ patients}$$

An additional analysis was performed to describe the reporting rate of opioid overdose events for patients with OUD (methods and results are presented in the electronic supplementary material).

3 Results

3.1 Identification of Cases of Opioid Overdose

During the 12-year period, 312 overdose cases were identified in the manufacturer's XR-NTX GSS database (Fig. 1). Of these, five case reports were excluded after narrative review: three cases because the patient did not receive XR-NTX and two case reports that each involved multiple patients (one case report with 12 patients and one case report with 15 patients) did not provide sufficient case detail to be adequately adjudicated in these analyses. Of the remaining 307 cases, 161 specifically attributed the overdose event to an opioid and 146 attributed the overdose event to another agent or did not provide information regarding the agent(s) used. Of the 161 cases attributed to opioid overdose, 66 cases (41% of opioid overdose case reports) were classified as assessable; of these, 57 cases were serious, and 40 of these cases were fatal. We were unable to conduct latency analyses on the remaining 95 individual-level data were excluded from the analysis as there was inadequate information to adjudicate these cases

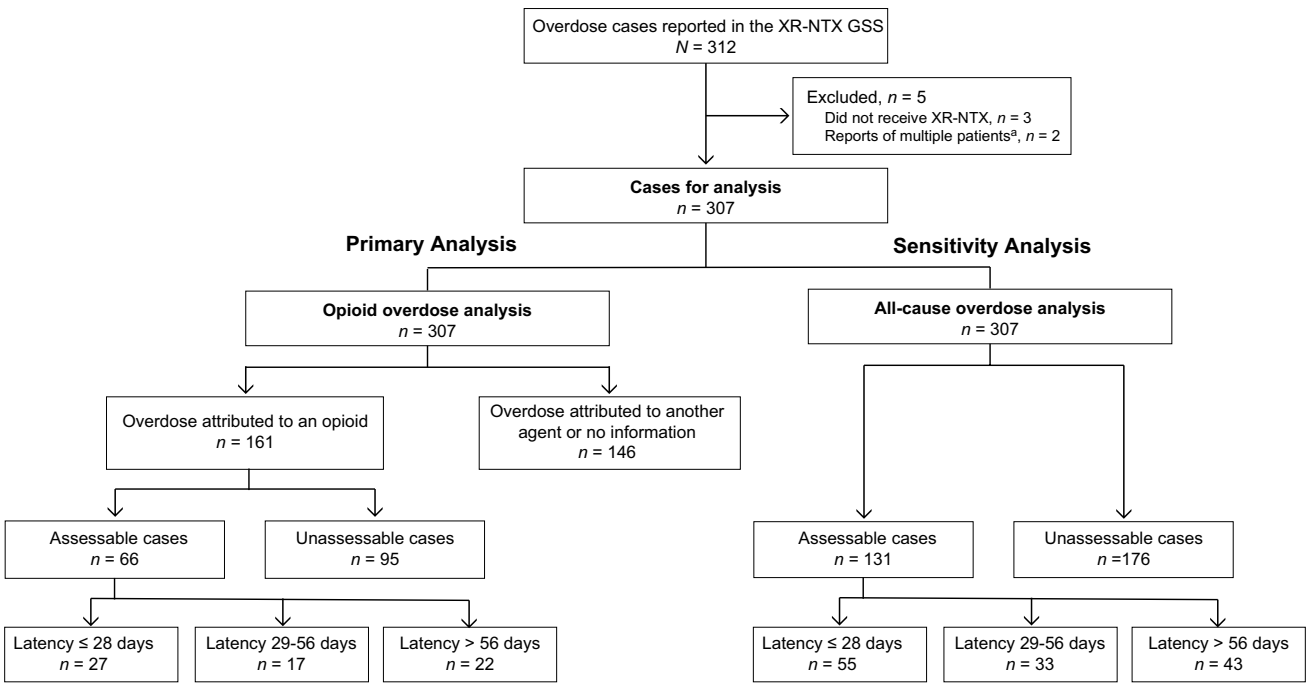

Fig. 1 Flow chart of identification of cases of opioid overdose and all-cause overdose. *GSS* global safety system, *XR-NTX* extended-release naltrexone. [a]Reports of multiple patients that did not report

opioid overdose case reports for which the period from the last dose could not be determined.

3.2 Reporting Rates for Opioid Overdose

The estimated reporting rates (per 10,000 patients exposed) for the 66 assessable cases were 0.54 (95% CI 0.36–0.79), 0.34 (95% CI 0.20–0.55), and 0.44 (95% CI 0.28–0.67) for ≤28 days, 29–56 days, and >56 days from the last dose of XR-NTX, respectively (Table 1). Reporting rates were <1/10,000 patients exposed among each latency grouping for assessable serious cases and for fatal cases (Table 1). Of note, half of assessable fatal opioid overdoses occurred >56 days from last XR-NTX dose.

To better understand the timing of reported opioid overdose events relative to the last XR-NTX dose, we calculated median event latency values for 63 of the 66 assessable cases (exact latency values could be calculated for 63 cases; for the remaining three cases, the latency value was approximate). Overall, the median event latency for all assessable cases approximated 32 days (range 1–145). For those cases of opioid overdose occurring >56 days from the last XR-NTX dose, the median latency was 76.5 days (range 60–145).

The estimated reporting rate for total cases (assessable and unassessable; 161 cases) was 3.25 (95% CI 2.77–3.79) per 10,000 patients exposed, and 87 of these cases were fatal, with an estimated reported rate of 1.75 (95% CI 1.41–2.17) per 10,000 patients exposed. We also calculated the reporting rate of opioid overdose for cases where event latency was determined to be unassessable (i.e., latency values could not be calculated): the estimated reporting rate for the 191 unassessable cases was 1.92 (95% CI 1.55–2.34) per 10,000 patients exposed.

3.3 Reporting Rates for All-Cause Overdose (Sensitivity Analysis)

Using a broader definition of opioid overdose events (i.e., all-cause overdoses, including opioids, non-opioids, and agent not specified), and considering the estimated proportion of patients treated for opioid dependence (approximately 50%), 131 cases were assessable for latency. The estimated reporting rates (per 10,000 patients) for the 131

Table 1 Number of cases and reporting rates of opioid overdose and all-cause overdose from April 2006 to April 2018

Time from last XR-NTX dose	Primary analysis	Sensitivity analysis
	Opioid overdoses in all patients treated for AUD or OUD	All-cause overdoses in patients treated for OUD (estimated)
All cases		
≤28 days	27 (0.54; 95% CI 0.36–0.79)	55 (2.22; 95% CI 1.67–2.89)
29–56 days	17 (0.34; 95% CI 0.20–0.55)	33 (1.33; 95% CI 0.92–1.87)
>56 days	22 (0.44; 95% CI 0.28–0.67))	43 (1.74; 95% CI 1.26–2.34)
Unassessable cases	95 (1.92; 95% CI 1.55–2.34)	176 (7.10; 95% CI 6.09–8.23)
Total cases	161 (3.25; 95% CI 2.77–3.79)	307 (12.39; 95% CI 11.04–13.85)
Serious cases		
≤28 days	22 (0.44; 95% CI 0.28–0.67)	44 (1.78; 95% CI 1.29–2.38)
29–56 days	13 (0.26; 95% CI 0.14–0.45)	28 (1.13; 95% CI 0.75–1.63)
>56 days	22 (0.44; 95% CI 0.28–0.67)	39 (1.57; 95% CI 1.12–2.15)
Unassessable cases	58 (1.17; 95% CI 0.89–1.51)	106 (4.28; 95% CI 3.50–5.17)
Total cases	115 (2.32; 95% CI 1.92–2.79)	217 (8.76; 95% CI 7.63–10.00)
Fatal cases		
≤28 days	12 (0.24; 95% CI 0.13–0.42)	23 (0.93; 95% CI 0.59–1 .39)
29–56 days	8 (0.16; 95% CI 0.07–0.32)	19 (0.77; 95% CI 0.46–1.20)
>56 days	20 (0.40; 95% CI 0.25–0.62)	35 (1.41; 95% CI 0.98–1.96)
Unassessable cases	47 (0.95; 95% CI 0.70–1.26)	88 (3.55; 95% CI 2.85–4.38)
Total cases	87 (1.75; 95% CI 1.41–2.17)	165 (6.66; 95% CI 5.68–7.76)

Data are presented as *n* (per 10,000 patients)

Unassessable cases were cases with incomplete information for dates

AUD alcohol use disorder, *CI* confidence interval, *OUD* opioid use disorder, *XR-NTX* extended-release naltrexone

N = 495,602 for opioid overdose; the number of patients exposed to XR-NTX was estimated based on XR-NTX units distributed and an estimated treatment persistence of 3.5 units per patient

N = 247,801 for all-cause overdose (assuming 50% of patients were treated for OUD)

assessable cases were 2.22 (95% CI 1.67–2.89), 1.33 (95% CI 0.92–1.87), and 1.74 (95% CI 1.26–2.34) for ≤28 days, 29–56 days, and >56 days from the last dose of XR-NTX, respectively (Table 1). Reporting rates were <10/10,000 patients exposed across each latency grouping for assessable serious cases and for fatal cases (Table 1).

4 Discussion

Opioid overdose reporting rates from cumulative XR-NTX postmarketing surveillance data from April 2006 to April 2018 provide evidence that reported opioid overdose rates, including those with fatal outcomes, were <10/10,000 patients exposed (and ranged from 0.16 to 0.54 per 10,000 patients exposed) among patients on XR-NTX treatment (≤28 days from the last XR-NTX dose), as well as across the periods of 29–56 days or >56 days after the last XR-NTX dose. In a sensitivity analysis, where all-cause overdose events (opioid overdose, non-opioid overdose, or cases where agent[s] was not reported) and only those patients treated for OUD (a 50% smaller population than all patients) were included, reporting rates remained <10/10,000 patients exposed across all latency periods (and ranged from 0.77–2.22 per 10,000 patients exposed).

We found that estimated rates of opioid overdose were similar across the three latency periods studied for assessable cases. The proportion of fatal opioid overdoses versus all opioid overdoses among each latency group was lowest in the on-treatment latency period (≤28 days; 12/27) and highest in the >56-day latency period (20/22). This nominal difference may be due to blockade of μ-opioid receptors during the on-treatment period versus no blockade after 56 days; however, differential reporting bias of fatal events across latency periods could also be a contributory factor. Overdose events occurring >56 days after last dose of XR-NTX likely reflect OUD event rates in an untreated population, which are reported to be greater than those for patients receiving medication treatment for OUD [17].

Prospective clinical trials of patients treated with XR-NTX have not demonstrated evidence of increased susceptibility to overdose compared with treatment as usual, placebo, or buprenorphine-naloxone treatment [28–33]. A 24-week randomized controlled, open-label, comparative effectiveness trial with 570 patients reported two fatal overdoses in the XR-NTX group and three in the buprenorphine-naloxone group (and 28 non-fatal overdoses: ten in the XR-NTX group, eight in the XR-NTX group that failed to initiate, nine in the buprenorphine-naloxone group, and one in the buprenorphine-naloxone group who failed to initiate), although—in the intent-to-treat analysis—the XR-NTX group had lower initiation and a higher relapse rate, largely due to failure to initiate [31]. In addition, a 12-week, open-label, clinical non-inferiority, randomized controlled trial in 159 patients found no overdoses in the XR-NTX group and one overdose in the buprenorphine-naloxone group [33]. In the 9-month extension phase of this study, there were no opioid overdoses in the group that transitioned to XR-NTX from buprenorphine ($n = 63$) and no opioid overdoses in the patients continuing on XR-NTX ($n = 54$) [32], although this was not a primary or secondary endpoint of the study. A randomized 24-week study of XR-NTX treatment in criminal justice offenders found no overdose events during treatment in the XR-NTX group ($n = 153$) and five overdose events in the treatment-as-usual (brief counseling and referrals for community treatment program, including agonist therapy if preferred or indicated; 37% received buprenorphine during the trial) group ($n = 155$) [30]. In addition, no overdoses were reported between XR-NTX discontinuation at 24 weeks and the end of the 52-week post-treatment follow-up, whereas two overdose events were reported in the treatment-as-usual group during the 52-week follow-up. However, comparative clinical trials have not been powered to demonstrate significant differences in overdose mortality, and treatment dropouts with loss to follow-up pose a challenge to data interpretation, particularly in the post-treatment discontinuation period. A prospective observational, open-label, single-arm, multicenter registry ($N = 395$) evaluating XR-NTX treatment in clinical practice during 2011–2013 did not demonstrate evidence of an increased susceptibility to opioid overdose in the months after last dose of XR-NTX; three overdose deaths were reported, which occurred 20 days, 2 months, and 4 months after the last XR-NTX dose [25].

Several published studies and a meta-analysis provide some limited clinical data regarding overdose risk after cessation of OUD treatment. In retrospective cohort studies, the period after cessation of medication has been shown to be a time of increased vulnerability to overdose, whereas remaining on treatment has been shown to decrease all-cause and overdose mortality [9, 11, 26, 34]. For example, analysis of a statewide claims database found that opioid overdose survivors treated with methadone or buprenorphine had a reduced risk of all-cause– and opioid-related mortality [9], and analysis of another claims database found that patients with OUD treated with methadone or buprenorphine had a reduced risk of opioid overdose [34]. Neither study found an association between naltrexone and mortality or overdose, but oral and XR-NTX were included and the event numbers were very low, which limited interpretation [9, 34]. However, results should be interpreted cautiously because of the limitations of administrative claim database analysis, the disproportionate distribution between the treatment groups, and the vastly differing rates of psychiatric comorbid conditions, all of which may confound the interpretation of the results.

A retrospective cohort study of 5646 opioid-dependent patients using data from the Western Australian Department of Health found that rates of fatal and nonfatal opioid overdoses were similar after cessation of treatment with buprenorphine (4.3 and 18.9 events per 1000 patient-years, respectively), methadone (2.6 and 21.3), and slow-release 6-month implant naltrexone (4.3 and 15.1) [15]. A meta-analysis of 30 cohort studies reported that patients who discontinued medication (buprenorphine, methadone, or long-acting implant naltrexone) had a higher risk of all-cause death (relative risk 2.33 [95% CI 2.02–2.67]) and overdose death (3.09 [95% CI 2.37–4.01]) than patients receiving medication [14]. However, a recent retrospective cohort study of commercially insured individuals did not find evidence of a higher overdose risk within the first 4 weeks after discontinuation of buprenorphine or naltrexone, although the sample size for XR-NTX was relatively small [26]. Collectively, this research demonstrates the importance of treatment continuation to decrease mortality risk in patients with OUD, regardless of treatment medication.

We are unaware of similar data analyses regarding opioid overdose reporting rates for other pharmacotherapies (i.e., methadone or buprenorphine) used for the treatment of OUD. However, a recent report by Saucier et al. [35] reviewed opioid overdose reporting rates following XR-NTX treatment. Saucier et al. [35] completed a retrospective case review of XR-NTX spontaneous reports over 5 years and 5 months (October 2010–March 2016) from FAERS and identified 52 fatal overdose cases (28 cases with a known interval from the last dose to overdose) with a reported median interval of 46 days (mean 56.3 days) from the last injection of XR-NTX to overdose and concluded that there was evidence of increased fatal overdoses in the second month following last dose of XR-NTX. In contrast, our current analysis used spontaneous reports from over 12 years, included both nonfatal and fatal events of opioid overdose, and found that reporting rates of opioid overdose during treatment with, or following discontinuation of, XR-NTX were similar and <10/10,000 patients exposed. The Saucier et al. [35] analysis excluded patients with only an alcohol indication and included any death due to overdose on opioids or an unspecified substance. Our sensitivity analysis of XR-NTX spontaneous reports over 12 years included evaluation of all overdose events (including opioid and non-opioid drug-related) and reporting rates using an estimate of only those patients assumed to be receiving XR-NTX for the opioid dependence indication (based on the subset of prescriptions for which Alkermes was informed of the indication), as indication is not reliably documented in case reports. Saucier et al. [35] hypothesized that there is a potential biologic "rebound effect," with increased susceptibility to overdose following the discontinuation of XR-NTX, but this is based on animal model data. This hypothesis is that chronic exposure to short-acting naltrexone may lead to an upregulation of opioid receptors in the mouse central nervous system [36, 37]. However, the relevance of this finding to an extended-release formulation, and the relevance of this finding to overdose risk in humans, is not supported by human laboratory data [38, 39] or clinical trial adverse event data [28–32, 40].

Our findings remain consistent with current XR-NTX prescribing information, which provides warnings regarding the vulnerability to opioid overdose, through attempting to overcome blockade during treatment, at the end of a dosing interval, after missing a dose, or after discontinuing XR-NTX. Given that OUD is a chronic, relapsing illness, adherence to medication is critical to prevent relapse and reduce associated risks.

Limitations of the current analysis are those common to any assessment using spontaneously reported safety data. These limitations include potential under- or over-estimation of the number of patients treated (the calculation was an estimate only and may not reflect the actual number of patients treated with XR-NTX for opioid dependence), under-reporting of events, non-representativeness, missing information (e.g., the opioid and/or non-opioid agents present in overdose), and inconsistent quality of data. For this study, missing information on the time from the last dose required the exclusion of a majority of reported overdose events and may have resulted in the under- or over-estimation of latency. Additionally, the estimation of the percentage of patients receiving XR-NTX related to opioid dependence may under- or over-estimate the actual proportion of patients treated for this purpose in the postmarketing setting, and the outcomes may be influenced by the lack of comparative retention rate data available for patients on XR-NTX (median three injections [25]) for opioid dependence or alcohol dependence. Furthermore, the recent rapid increase in the abuse of potent synthetic opioid analogs may make cumulative data less generalizable to the current state of the opioid overdose epidemic in the USA [41]; however, approximately 60% of all XR-NTX prescribed from product approval through 2018 had been prescribed (and overdose reports received) between 2016 and 2018. Finally, reporting bias likely contributed to differential under-reporting across latency periods, particularly with greater likelihood of overdose event under-reporting occurring in the more remote periods from the last XR-NTX use.

5 Conclusions

This analysis of 12 years of cumulative postmarketing data for XR-NTX illustrates that reporting rates of opioid overdose events were <10/10,000 patients exposed

while on treatment (0.54 per 10,000 patients exposed) and occurred at similar rates ≥29–56 days (0.34 per 10,000 patients exposed) or >56 days (0.44 per 10,000 patients exposed) following last dose of XR-NTX. Although our analysis has limitations associated with analysis of spontaneous report data, our findings are consistent with overdose event data reported from clinical trials of participants with OUD, which, although limited, have not demonstrated evidence of an increased rate of overdose with XR-NTX compared with treatment as usual, placebo, or buprenorphine. With the ongoing rise in opioid overdose rates in the USA, further research is needed to characterize mortality risk during and following treatment with XR-NTX and other medications used to treat OUD and to identify methods that improve treatment retention and thereby mitigate the opioid overdose risk associated with untreated OUD.

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Declarations

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Conflict of interest Kimberley McKinnell, Prashanthi Vunnava, Avani Desai, Madé Wenten, James Fratantonio, Sarah C. Akerman, Maria A. Sullivan, Gary Bloomgren are current employees of Alkermes, Inc. and may hold stock in Alkermes, Inc. Rose Marino, Priya Jain, and Marie A. Liles-Burden are former employees of Alkermes, Inc.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent to Publication Not applicable.

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