LONG-ACTING NALTREXONE HAS LONG-ACTING BENEFITS AND 100% INDUCTION RATES ARE NOT DIFFICULT TO ACHIEVE

Jarvis et al.’s comprehensive review of Vivitrol (extended-release-naltrexone/XR-NTX) [1] included three important clinical issues worth expanding. First, their discussion of low ‘rates of induction’ onto XR-NTX, defined as the percentage of those offered XR-NTX who received their first injection, ignores evidence from studies of implanted NTX that intention-to-treat induction rates of 100% have been routinely and safely achieved for many thousands of patients with relatively simple techniques [2–4], including one that requires no nursing or medical presence. To describe induction procedures lasting 7–8 days as ‘rapid’ suggests unfamiliarity with these methods, which eliminate what is perhaps the biggest obstacle to wider use of XR-NTX. Carreño et al.’s definition of ‘rapid’ induction techniques (those that, inter alia, enable patients to have taken full therapeutic doses of NTX within 24 hours) [5] has not been disputed. Secondly, quantifying ‘opioid use’ by ‘the percentage of urine samples negative for opioids’ is arguably an inappropriate sole measure of opioid intake in patients receiving adequate doses of XR-NTX because (unlike patients on agonist maintenance) NTX patients usually develop no agonist effects from even large doses of opioids [6,7]. Continued use of opiates despite complete blockade is an interesting and challenging phenomenon [7–11], but compatible with complete abstinence from opiates at the neuropharmacological level. Even persistent opiate use (usually intravenous) during the first weeks of parenteral NTX treatment sometimes disappears eventually. Habit and curiosity often drive early use. That curiosity may reflect hopes that the blockade can be over-ridden, or is waning, but it often reflects understandable needs for reassurance that NTX really does block opiates, thus reinforcing initially fragile beliefs in the possibility of remaining opiate-free for long enough for new opiate-free habits to become both automatic and effortless [12].

This leads to the third issue. They note, correctly, that other forms of XR-NTX can provide opiate blockade for as much as 7 months, but the crucial clinical relevance of this advantage is obscured by their claim that ‘the effects of XRNTX have been shown not to persist once discontinued’. On both theoretical and empirical grounds, that claim is questionable except for very short-term treatment. Patients who persist with XR- or implanted NTX are, by definition, ‘good compliers’ and thus more likely to do well when NTX is discontinued [13]. Furthermore, being unable to experience agonist effects for several months, rather than having to decide every month to continue treatment (or not), makes it more likely that patients will adapt to opiate-free habits even if their motivation was initially poor. We have previously noted the many (largely unrecognized) similarities between disulfiram in alcohol dependence and NTX in opiate dependence. In the remarkably successful Out-patient Long-term Intensive Therapy for Alcoholics (OLITA) alcoholism programme, patients took supervised disulfiram for an average of about 3 years but 75% were still abstaining after 9 years [14]. In a British audit of long-acting NTX implants, 52% of patients who had one implant (and 100% of those who had two) remained opiate-free at 24 months, long after opiate-blockade had disappeared [15].

Declaration of interests

None.

**Keywords** Induction rates, long-acting naltrexone, naltrexone, naltrexone-induction, opiate antagonist, opiates.

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The authors could be investigated for their utility in increasing XR-NTX induction. However, those described in our review, could be investigated for acting NTX formulations. Induction procedures for other extended-release injectable naltrexone (XR-NTX) [2]. As stated in our methods, we intentionally focused on studies using XR-NTX and did not consider studies on other long-acting NTX formulations. Induction procedures for other long-acting NTX formulations, if more successful than those described in our review, could be investigated for their utility in increasing XR-NTX induction. However, the authors’ claim that 100% intent-to-treat induction rates for implantable NTX have been routinely achieved for thousands of patients is not supported by the cited reports. Two of these reported induction onto oral NTX [3,4]. The other [5] was a retrospective report of two cohorts, which were both comprised of patients who had previously received implantable NTX; induction rates were not reported. We described induction procedures as ‘rapid’ because these involved XR-NTX administration before the manufacturer-recommended 7–10 days of opioid abstinence [6]. In our search, we did not identify any published studies investigating shorter XR-NTX inductions within 24 hours. The suggestion by Brewer & Streel that induction to XR-NTX can routinely be easy and rapid is out of touch with broad experience to the contrary. For example, a recent multi-site clinical trial [7] that was included in our review from the US National Drug Abuse Treatment Clinical Trials Network referred to the relative difficulty of beginning XR-NTX versus sublingual buprenorphine–naloxone (significant at P < 0.0001) as ‘a substantial induction hurdle’. Regarding our decision to report urinalysis data we agree that, while guidelines are available [8], there is no single standard for the selection of primary outcome measures for clinical trials evaluating medications for opioid use disorder [9]. We chose to measure opioid use as the percentage of urine samples negative for opioids because this is nearly universally collected in clinical trials, and provides an objective measure of recent opioid use. Several of the clinical trials included in our review used other opioid use outcomes (e.g. relapse, self-reported opioid-free days). We reported these findings and considered them in our conclusions on XR-NTX’s efficacy and effectiveness. Brewer & Streel’s statement that opioid use during XR-NTX blockade might constitute a ‘neuropsychological abstinence’ is valid, but of unclear relevance. When adhered to, XR-NTX affords protection from overdose and agonist effects that might interfere with normal activities (e.g. driving, working, taking care of children), but opioid use can still have considerable negative impacts when taken under XR-NTX blockade (e.g. spread of HIV/HCV, infection, exposure to legal consequences, financial problems). These consequences should be emphasized, even if further evidence confirms an extinction-based mechanism for XR-NTX’s effectiveness [10]. Our statement that XR-NTX’s therapeutic effects on opioid use do not persist once discontinued was based on a large 24-week multi-site randomized controlled trial with follow-up at 52 and 78 weeks [11]. This finding and our statement are consistent with the chronic, relapsing nature of opioid use disorder and mirror the much larger literature on the effects of adherence to methadone and buprenorphine on opioid use [12]. Rather than obscuring the clinical effects of XR-NTX, as suggested by Brewer & Streel, we believe this finding highlights the critical

EXTENDED-RELEASE INJECTABLE NALTREXONE (XR-NTX): A RESPONSE TO CLINICAL ISSUES RAISED BY BREWER & STREEL

We appreciate the letter by Brewer & Streel [1] expanding on clinical issues reported in our recent review on extended-release injectable naltrexone (XR-NTX) [2]. As stated in our methods, we intentionally focused on studies using XR-NTX and did not consider studies on other long-acting NTX formulations. Induction procedures for other long-acting NTX formulations, if more successful than those described in our review, could be investigated for their utility in increasing XR-NTX induction. However, the authors’ claim that 100% intent-to-treat induction