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Patient preferences and extended-release naltrexone: A new opportunity to treat opioid use disorders in Ukraine

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ABSTRACT

Background: Scaling up HIV prevention for people who inject drugs (PWID) using opioid agonist therapies (OAT) in Ukraine has been restricted by individual and structural factors. Extended-release naltrexone (XR-NTX), however, provides new opportunities for treating opioid use disorders (OUDs) in this region, where both HIV incidence and mortality continue to increase.

Methods: Survey results from 1613 randomly selected PWID from 5 regions in Ukraine who were currently, previously or never on OAT were analyzed for their preference of pharmacological therapies for treating OUDs. For those preferring XR-NTX, independent correlates of their willingness to initiate XR-NTX were examined.

Results: Among the 1613 PWID, 449 (27.8%) were interested in initiating XR-NTX. Independent correlates associated with interest in XR-NTX included: being from Mykolaiv (AOR = 3.7, 95% CI = 2.3–6.1) or Dnipro (AOR = 1.8, 95% CI = 1.1–2.9); never having been on OAT (AOR = 3.4, 95% CI = 2.1–5.4); shorter-term injectors (AOR = 0.9, 95% CI 0.9–0.98); and inversely for both positive (AOR = 0.8, CI = 0.8–0.9), and negative attitudes toward OAT (AOR = 1.3, CI = 1.2–1.4), respectively.

Conclusions: In the context of Eastern Europe and Central Asia where HIV is concentrated in PWID and where HIV prevention with OAT is under-scaled, new options for treating OUDs are urgently needed.

Findings: here suggest that XR-NTX could become an option for addiction treatment and HIV prevention especially for PWID who have shorter duration of injection and who harbor negative attitudes to OAT. Decision aids that inform patient preferences with accurate information about the various treatment options are likely to guide patients toward better, patient-centered treatments and improve treatment entry and retention.

1. Introduction

The Eastern European and Central Asian region remain the only region globally where HIV incidence and mortality continue to increase (Joint United Nations Programme on HIV/AIDS (UNAIDS, 2016a). Ukraine's HIV epidemic, emblematic for the region, remains concentrated in people who inject drugs (PWID), mostly of opioids, and in their sexual partners (Kiriazova et al., 2013; Mazhnaya et al., 2014). High methadone coverage is the most cost-effective strategy to avert new HIV infections in Ukraine (Alistar et al., 2011), including in prisoners (Altice et al., 2016). Scale-up of opioid agonist therapies (OAT) in Ukraine began with the introduction of maintenance therapy using buprenorphine (BMT) in 2004 (Bruce et al., 2007), followed by methadone (MMT) in 2008 (Lawrinson et al., 2008). OAT scale-up has not, however, increased appreciably since 2010, despite targets to provide OAT at no cost to 20,000 PWID by 2015 (Dutta et al., 2013); currently only 2.7% of the 340,000 PWID are prescribed it (Degenhardt et al., 2014; Wolfe et al., 2010). Numerous individual and structural factors have impeded OAT scale-up in Ukraine (Bojko et al., 2013,2015,2016; Izenberg et al., 2013; Mazhnaya et al., 2016; Mimiaga et al., 2010), including negative attitudes toward OAT by both patients and providers (Bojko et al., 2015; Makarenko et al., 2016,2017b; Polonsky et al., 2015,2016c). MMT and BMT were introduced in Ukraine initially for the prevention of HIV, and not for the treatment of opioid use disorders

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Extended-release naltrexone (XR-NTX) was approved to treat alcohol dependence in Ukraine in 2008 and opioid use disorders in 2014. XR-NTX, however, was introduced commercially, unlike MMT and BMT the other two evidence-based medication-assisted therapies (MAT) introduced in 2004 and 2008 for treating opioid use disorders. Because XR-NTX is a complete opioid antagonist, it does not require patients to undergo official "registration" as a drug user, which often results in the loss of one's driver's license, employment restrictions (Bojko et al., 2013; Bojko et al., 2015) and promotes police harassment (Bojko et al., 2015; Izenberg et al., 2013; Kutsa et al., 2016; Polonsky et al., 2016a). Once-monthly injections overcome such structural barriers as daily transportation for direct supervision (Alanis-Hirsch et al., 2016; Cousins et al., 2016), but are costly to patients because they are not supported by international donors or provided free by the government.

In March 2016, the Ministry of Health Order 200 that regulates OAT delivery was changed, allowing OAT to be prescribed outside addiction specialty settings, for purchase in pharmacies and take-home doses allowed for 7-10 days. This change opened new opportunities for XR-NTX patients who can now avoid inpatient supervised withdrawal ("detox") and can taper off opioids using buprenorphine purchased in ambulatory settings. Given the current treatment milieu, XR-NTX can also be administered to incarcerated persons transitioning to the community within inpatient programs that "detox" patients. XR-NTX, as a complete opioid antagonist, might overcome negative attitudes toward OAT (Polonsky et al., 2016c) and be attractive to patients and providers. It also may provide new opportunities for concomitant treatment for patients with both alcohol and opioid use disorders, which co-occur often in Ukraine (Azbel et al., 2013). Last, its pharmacological properties avoid sedation and drug interactions with HIV or tuberculosis medications (Altice et al., 2010), and when not interrupted, prevent overdose.

In the presence of suboptimal OAT scale-up and a changing legal landscape for addiction treatment, we analyzed survey data from an implementation science study focusing on the expansion of MAT in Ukraine. Specifically, the objectives of the study were to better understand PWID's knowledge about and willingness to receive XR-NTX as an alternative MAT to treat opioid use disorders in Ukraine and to inform patient preferences and alternative strategies for treating opioid use disorders and to guide how to clinically position XR-NTX as an additional strategy to prevent HIV in this especially volatile region where HIV is concentrated in PWID (Joint United Nations Programme on HIV/AIDS (UNAIDS, 2016a).

2. Methods

2.1. Study design

Detailed methods for the cross-sectional survey have been published previously (Makarenko et al., 2016,2017b). Briefly, from January 2014 to March 2015, PWID 18 years or older and meeting ICD-10 criteria for OUDs were randomly recruited from five geographically distinct regions of Ukraine. Participants were stratified by their OAT status: 'currently', 'previously', or 'never' on OAT. PWID who were never on OAT were recruited using respondent-driven sampling, while current and previous OAT clients were randomly selected from OAT treatment rosters. Surveys were developed based on formative focus group data, self-administered and collected online using Qualtrics®. A standardized script was provided that described the objective attributes of XR-NTX. The instructions for respondents provided by the interviewer stated, "Naltrexone is a full antagonist of opioid receptors. This means the medication can block receptors and doesn't allow a person to get high after using heroin or other opioid agonists like morphine, codeine, methadone, etc. Naltrexone is a medication that can be administered as tablets every day. There is also a form of naltrexone, which can be injected and continues to work for about one month. This is extended-release naltrexone is called Vivitrol. After the injection, a person can't get high from using heroin or other opioid agonists during the month when Vivitrol is within the body." Trained research assistants were available to clarify any survey item meanings and provide technical assistance. XR-NTX questions assessed awareness of, interest in, and preference for receiving this type of MAT. Participants were compensated 100UAH (~$4) for survey completion. Few, if any, participants approached refused study participation.

2.2. Measures

In addition to demographic and social characteristics, the survey assessed drug use and treatment experiences, HIV status and testing, and standardized measures of alcohol use disorders (Saunders et al., 1993), depression (CES-D) (Radloff, 1977), addiction severity (DAST-10) (Gavin et al., 1989), and health-related quality of life (HRQoL) (Ware et al., 1996). HIV and HCV testing and post-test counseling were conducted by licensed medical staff using rapid tests (CITO TEST HIV 1/2/0 and CITO TEST HCV).

Willingness to initiate XR-NTX was the primary outcome. This was assessed by asking respondents if they could choose any MAT available to treat their opioid use disorder, which of the following would they choose to initiate now (all are available in Ukraine): 1) daily sublingual buprenorphine tablet, 2) daily buprenorphine injection, 3) daily methadone tablet, 4) daily methadone liquid, 5) oral naltrexone, or 6) once-monthly XR-NTX injection. For the current analysis we constructed a binary outcome variable, XR-NTX vs. all other available treatment options. Binary and independent correlates of a preference for XR-NTX versus any other treatment option are presented in Table 1. Age and years of drug injection were continuous. The following were binary: last 30-day drug injection frequency ($>$ 20 days versus $\leq$ 20 days), alcohol use disorders (AUDIT $\geq$4 for women and $\geq$8 for men) (Saunders et al., 1993), moderate/severe addiction severity (DAST-10 $\geq$3)(Gavin et al., 1989), moderate/severe depression (CES-D $>$ 10)(Radloff, 1977) and previous incarceration. We used previously published methods (Makarenko et al., 2016; Polonsky et al., 2016a,2016b,2016c) for creating two continuous composite variables reflecting both "positive" and "negative" attitudes toward OAT (MMT or BMT).

2.3. Statistical analysis

After bivariate analyses were performed using chi-square test for categorical variables and *t*-test for continuous variables, backwards selection was used in the multivariable logistic regression to identify independent factors associated with being willing to initiate XR-NTX, with covariates significant at $p < 0.10$ in bivariate analyses being included in the final model. This analytical strategy provided the best goodness-of-fit relative to other models. Data for all analyses were weighted based on population estimates in each type of OAT experience (currently on, previously on, and never on OAT) for each city sampled. The population estimates for two OAT groups were derived from OAT registries, while the population size of PWID never on OAT was derived from national estimates, and adjusted based on our sample selection of PWID (Berleva et al., 2012). Weighted multivariable logistic regressions were used to analyze the primary outcome of preferring XR-NTX compared to all other types of MAT. All analyses were conducted in SAS version 9.3 (SAS Institute, Cary, NC).

2.4. Ethical oversight

The study was approved by institutional review boards at Yale University and the Gromashevskiy Institute at the National Academy of Medical Sciences.