Chasing the Dragon Away: Personality as a protective factor and extended-release naltrexone as a treatment for heroin dependence
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Chapter 3

Acceptability of extended-release naltrexone by heroin dependent patients and addiction treatment providers in The Netherlands

Eline R. Zaaijer, Anna E. Goudriaan, Maarten W.J. Koeter, Jan Booij, Wim van den Brink

Submitted
Abstract

Extended-release naltrexone (XRNT) was developed to overcome poor treatment compliance with oral naltrexone in alcohol and opioid dependent patients. XRNT injections are registered in the USA and Russia, but not in The Netherlands. This study evaluates the support for abstinence oriented treatment among heroin dependent patients and the acceptability of XRNT injections by heroin dependent patients and treatment providers in The Netherlands. A sample of 261 patients in methadone maintenance treatment or heroin assisted treatment and a sample of 188 addiction treatment providers completed specially designed questionnaires. The current study shows that many patients in opioid maintenance treatment (58%) report a desire to become abstinent from opioids and that 83% of the patients with a desire for abstinence are interested in XRNT. The majority of treatment providers (81%) are willing to support the prescription of XRNT injections in opioid dependent patients to prevent relapse after detoxification. The current practice of automatic and indefinite continuation of opioid substitution should therefore be reconsidered. It should be noted, however, that XRNT injections are very expensive and currently not reimbursed by the health insurance agencies in The Netherlands.

Keywords: heroin dependence, extended-release naltrexone, patient preference, personal recovery, abstinence, acceptability
1. Introduction

Heroin dependence is a worldwide problem causing enormous suffering to those afflicted and their loved ones and is associated with substantial societal costs (1,2). In The Netherlands (16.7 million inhabitants), there are about 14,000 problematic heroin users (3). The vast majority (85-90%) does not inject but inhales their heroin [“chasing the dragon”: (4,5)]. About 80% of all the problematic heroin users in The Netherlands is in regular contact with the addiction treatment system: 85% in methadone maintenance treatment, 5% in heroin assisted treatment, and 10% in abstinence oriented treatment (3,6). Thus, treatment of this patient group is mainly aimed at harm reduction, and not at immediate abstinence. However, internationally, there has been a significant shift towards recovery-oriented drug treatment (7), with the final goal of enduring abstinence (8). Detoxification followed by oral naltrexone treatment and social rehabilitation has been the preferred strategy to reach this goal (9). However, this strategy has not been very successful (10), mainly due to the low compliance with oral naltrexone (11). Extended-release naltrexone (XRNT), given as an intramuscular injection or a subcutaneous implant, may create new opportunities. Several studies using implants have shown positive results (for a review see: (12)). Similarly, patients receiving XRNT injections stay in treatment longer than patients receiving placebo injections (for reviews see: (13–15)), and XRNT injections significantly reduce heroin use, decrease craving and prevent relapse (for reviews see: (11,13,16)). XRNT injections are approved in the USA and Russia for use in opioid dependent patients, but are not yet registered in most European countries, including The Netherlands. Moreover, little is known about the acceptability of XRNT injections by heroin dependent patients and treatment providers.

A small study by Fishman et al. (2010) among opioid dependent adolescents and young adults in the USA found that patients, as well as family members, accept the use of XRNT and that parents are enthusiastic about the concept of blockade and feel relieved by the anticipated control. Reasons that were given to decline the use of XRNT included aversion to medication treatment or injections, preference for buprenorphine and problems with insurance (17). Similarly, a study in Scotland showed that around 75% of heroine dependent patients starting a new episode of drug treatment wanted to become abstinent (18).

In The Netherlands, there seems to be little enthusiasm for a new abstinence-oriented drug treatment, both among patients and addiction treatment providers. This is also expressed in the fact that most treatments for heroin dependent patients in the Netherlands are aimed at harm reduction through methadone maintenance treatment or heroin assisted treatment. However, the question whether more abstinence oriented treatments are wanted has not been properly studied yet.
Therefore, the aim of the current study is to explore the support for abstinence oriented treatments among patients and to evaluate the acceptability of XRNT injections as a new treatment option by patients and addiction treatment providers.

2. Methods

2.1 Study population

Between March 1 2012 and June 30 2013, 261 patients completed a specially designed questionnaire (see below). Patients were recruited from three different addiction treatment centers in the two largest cities in The Netherlands: Amsterdam and Rotterdam. They were approached by a researcher or by their treatment provider. The questionnaires were completed by the patients, supported by the research assistant if needed. After completing the questionnaire, patients were compensated for their efforts with five euros.

Between March 1 2012 and December 31 2013, 188 addiction treatment providers from several addiction treatment centers throughout The Netherlands completed an online, anonymous questionnaire that was sent out through addiction treatment organizations, inviting professionals to participate.

The Ethical Committee of the Academic Medical Centre of the University of Amsterdam confirmed that the Medical Research Involving Human Subjects Act did not apply to the questionnaire for heroin dependent patients. All patients gave informed consent for their participation in the study.

2.2 Assessments

The questionnaires for patients and treatment providers were based on the Dutch version of the Addiction Severity Index (ASI: (19)), the Measurements in the Addictions for Triage and Evaluation (MATE: (20)) and on a review of the literature on acceptability of XRNT (17,18,21–23).

The anonymous questionnaire for patients collected information on the use of heroin and other drugs, physical illness, psychiatric symptoms, income, housing, addiction treatment and interest in XRNT, and contained multiple choice items, sometimes with an optional explanation. Completing the questionnaire generally took about 15 minutes.

The anonymous questionnaire for treatment providers collected information about their working experience in addiction treatment, experience with naltrexone, willingness to prescribe XRNT and about their expectation of the willingness of patients to take XRNT. The questionnaire comprised both multiple choice and open ended items. Completing the questionnaire took about 5 minutes.
2.3 Statistical analyses
To determine whether the patients with a desire for abstinence significantly differed on socio-demographic characteristics from patients with no desire for abstinence, two-sample independent t-tests and chi-squared/Fisher’s Exact tests were used for continuous and categorical variables, respectively. Univariate logistic regression analysis was used to obtain odds ratios (OR) with 95% confidence intervals (95% CI) in order to determine the predictors for ‘interest in treatment with XRNT injections among opioid dependent patients’ and for ‘willingness to prescribe XRNT among treatment providers’ and their ‘expectation that patients want treatment with XRNT’.

We used a significance threshold of .01 instead of .05 to correct for multiple testing without losing too much power. Although this implies an elevated family wise error, we believe that in this kind of explorative studies the type I error is not more important than a type II error. All statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) version 20.

3. Results
3.1 Heroin dependent patients
A total of 261 patients were recruited. The mean age of this group was 49.0 years (SD 7.4). Eighteen patients (6.9%) were excluded due to missing values. Of the remaining 243 patients, 103 were in methadone maintenance treatment, 4 in buprenorphine maintenance treatment and 136 in heroin-assisted treatment (heroin+methadone).

When asked whether they would be interested in a new kind of treatment aimed at the complete cessation of heroin and methadone use, 58.4% (N=142) answered ‘yes’, 28.0% (N=68) answered ‘no’ and 13.6% (N=33) had ‘no opinion’.

Table 1 shows that compared to patients with no desire for abstinence, patients with a desire for abstinence tended to start their use of heroin about two years later (21.3 vs. 23.3 years; \( p = 0.023 \)) and also tended to use heroin shorter than patients with no desire for abstinence (22.1 vs. 18.9 years; \( p = 0.013 \)), but both groups were using heroin for about 20 years. Significantly more patients with no desire for abstinence were in heroin-assisted treatment, compared to the patients with a desire for abstinence (67.3% vs. 47.9%; \( p = 0.004 \)).

The 142 patients who were interested in a new kind of treatment aimed at the complete cessation of heroin and methadone use were provided with some information regarding the working mechanism of XRNT. Next they were asked whether they would be interested to take this medication [XRNT] as an aid to completely stop using heroin and methadone. A total of 118 patients (83.1% of the 142) answered affirmative. Table 2 shows that none of the investigated characteristics was significantly associated with the interest in treatment with XRNT.
Table 1. Socio-demographic and drug use characteristics of heroin dependent patients

<table>
<thead>
<tr>
<th></th>
<th>Desire for abstinence (N=142)</th>
<th>No desire for abstinence* (N=101)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>82.4%</td>
<td>87.1%</td>
<td>0.317</td>
</tr>
<tr>
<td>Caucasian</td>
<td>53.5%</td>
<td>50.5%</td>
<td>0.642</td>
</tr>
<tr>
<td>Age first heroin use (mean + SD)</td>
<td>23.3 (7.5)</td>
<td>21.3 (6.3)</td>
<td>0.023</td>
</tr>
<tr>
<td>Duration of heroin use</td>
<td>18.9 (9.9)</td>
<td>22.1 (9.7)</td>
<td>0.013</td>
</tr>
<tr>
<td>Use of other drugs in last 12 months(^c)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine or base coke/crack</td>
<td>69.7%</td>
<td>74.3%</td>
<td>0.439</td>
</tr>
<tr>
<td>Amphetamine/speed</td>
<td>4.2%</td>
<td>3.0%</td>
<td>0.739</td>
</tr>
<tr>
<td>Cannabis/hashish/weed</td>
<td>41.5%</td>
<td>37.6%</td>
<td>0.538</td>
</tr>
<tr>
<td>XTC</td>
<td>3.5%</td>
<td>2.0%</td>
<td>0.703</td>
</tr>
<tr>
<td>LSD or magic mushrooms</td>
<td>1.4%</td>
<td>0%</td>
<td>0.512</td>
</tr>
<tr>
<td>Sleeping pills or sedatives</td>
<td>39.4%</td>
<td>36.6%</td>
<td>0.658</td>
</tr>
<tr>
<td>None of the above</td>
<td>7.7%</td>
<td>12.9%</td>
<td>0.187</td>
</tr>
<tr>
<td>Current treatment</td>
<td></td>
<td></td>
<td>0.004*</td>
</tr>
<tr>
<td>Methadone maintenance treatment</td>
<td>50.7%</td>
<td>30.7%</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine maintenance treatment</td>
<td>1.4%</td>
<td>2.0%</td>
<td></td>
</tr>
<tr>
<td>Heroin-assisted treatment: heroin +methadone</td>
<td>47.9%</td>
<td>67.3%</td>
<td></td>
</tr>
<tr>
<td>Previous treatment with oral naltrexone</td>
<td>1.4%</td>
<td>2.0%</td>
<td>0.999</td>
</tr>
</tbody>
</table>

\(^a\) total of ‘no desire for abstinence’ (N=68) and ‘no opinion’ (N=33)

\(^b\) a subject was considered Caucasian when both parents originated from a European country or the USA and non-Caucasian otherwise

\(^c\) more than 5 times used in last 12 months

\(^d\) p value for all three categories of current treatment

Finally, patients were asked to give an explanation for their answer using an open ended question. Several benefits and disadvantages were mentioned. With regard to the benefits of XRNT treatment, several patients felt that a new drug would motivate them again to try to stay abstinent following detoxification after a lot of failed attempts. Many patients reported to be dissatisfied with their methadone maintenance treatment, they mainly complained that it takes a lot of time to pick up the medication and about its side effects (mainly drowsiness during the day). Other complaints about methadone were that it is very addictive and that it does not work the whole day. With regard to the disadvantages of XRNT treatment, a few patients mentioned that they worried about side effects of XRNT (anhedonia, overdose of heroin) and some would not take XRNT because they did not want to take any medication anymore, because they had bad experiences with oral naltrexone, because they were afraid of injections, because they were afraid that XRNT would also be addictive or because they thought that abstinence of two weeks before starting XRNT treatment was impossible. Several patients mentioned that they
would like to have more information about XRNT or that they would first like to hear positive experiences from others before they would consider treatment with XRNT.

### 3.2 Addiction treatment providers

Of the 188 addiction treatment providers, 11 did not fully complete the questionnaire. The remaining 177 (94.1%) were included in the analyses: addiction medicine physicians (44.6%), psychiatrists (6.2%), psychologists (13.0%), nurses (17.5%), others (18.6%). Of them, 143 (80.8%) would support the prescription of XRNT and 139 (78.5%) expected that patients wanted to be treated with XRNT. Treatment providers willing to support the prescription of XRNT worked shorter in addiction treatment services than those not willing support XRNT prescription (8.9 (SD 7.7) years vs. 13.0 (SD 10.2) years; OR=0.95, 95% CI 0.91–0.99, p=0.014). ‘Experience with the prescription of oral naltrexone’ was not predictive of their willingness to prescribe XRNT (p=0.327). Neither career duration nor experience with the prescription of oral naltrexone were predictive of the expectation that patients would want XRNT treatment (p=0.905 and p=0.501, respectively).

The 143 treatment providers willing to support the prescription of XRNT were also asked to which patients they would prescribe XRNT (multiple answers possible). Most of these treatment providers were willing to prescribe XRNT to both patients with previous experience with oral naltrexone (82.5%) and to patients with no previous experience with oral naltrexone (64.3%). About half of the treatment

<table>
<thead>
<tr>
<th>Table 2. Predictors for patient’s interest in XRNT treatment</th>
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<tbody>
<tr>
<td>Interest in XRNT (N=118)</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Caucasian</td>
</tr>
<tr>
<td>Age first heroin use (mean + SD)</td>
</tr>
<tr>
<td>Duration of heroin use (mean + SD)</td>
</tr>
<tr>
<td>Having a serious or contagious disease</td>
</tr>
<tr>
<td>Psychological or psychiatric treatment in the past year</td>
</tr>
<tr>
<td>Having a job</td>
</tr>
<tr>
<td>Number of nights last 30 days spent in own house</td>
</tr>
<tr>
<td>Total number of previous treatments</td>
</tr>
<tr>
<td>Longest period of abstinence during treatment (months)</td>
</tr>
<tr>
<td>Satisfied with current treatment outcome</td>
</tr>
</tbody>
</table>

* Univariate logistic regression with interest in XRNT (yes/no) as dependent and listed predictors as independent variables
providers were willing to treat opiate dependent patients with XRNT currently in methadone maintenance treatment (58.7%), whereas a minority of the providers thought that XRNT was also a good idea for heroin users without previous treatments (32.2%) or for patients currently in heroin-assisted treatment (25.9%).

Treatment providers were also asked whether they were satisfied with the existing opioid agonist maintenance treatments (methadone, buprenorphine, heroin-assisted treatment). The main benefit of these treatments mentioned was that patients have a more stable life. Disadvantages that were mentioned more than once were: methadone dependence, interaction with other medications, emotional flattening, possibility of continued illicit heroin use and the drug-related cues that patients encounter when they visit the methadone/heroin clinic.

Next, treatment providers were asked whether they were satisfied with detoxification of heroin dependent patients followed by relapse prevention with oral naltrexone. Most treatment providers stated that compliance is a problem, and that many patients relapsed into illicit heroin use. They commented that supervised intake or extended release formulations would give better results, and that oral naltrexone is only suitable for highly motivated patients. Another reported disadvantage was side effects of oral naltrexone (general malaise, anhedonia).

Finally, treatment providers were asked whether they would support prescribing XRNT to their patients as a possibility to prevent relapse after successful detoxification. Many treatment providers stated that XRNT should only be prescribed to patients who are eligible for abstinence oriented treatment, who are very highly motivated, who have social support and who already have experience with oral naltrexone. Some treatment providers were afraid of overdose after quitting naltrexone treatment and about the problems related to emergency pain management and some would only prescribe XRNT to heroin dependent patients without (frequent) cocaine use. Several treatment providers mentioned that they would like to have more information about the risks of XRNT treatment before deciding whether they would want to prescribe XRNT or not.

4. Discussion

The current study shows that in the Netherlands, where most of the treatment seeking problematic heroin users are in methadone maintenance or heroin-assisted treatment, 58% of the patients report a desire to become abstinent from all opioid agonists, that 83% of those with a desire for abstinence is interested in XRNT, and that 81% of the treatment providers supported the prescription of extended-release naltrexone (XRNT) to prevent relapse after detoxification.

These findings are consistent with studies from other countries. In Scotland, McKeganey and co-workers found that about three-quarters of all treatment seeking heroin patients were interested in treatments directed at total abstinence with no
sex difference in the wish to become abstinent (18). Moreover, a small study in the USA among opioid dependent adolescents and young adults found that patients and family members accepted XRNT as a promising treatment (17).

In contrast to the study by Friedmann et al. among homeless alcohol dependent patients in the USA (23), fear of the XRNT injections is only reported by some of our patients. Moreover, most of the disadvantages of methadone treatment mentioned by our patients (e.g. time consuming, side effects, addictive) are also described in the study by Neale (24). It therefore seems important to give more information to patients about XRNT to make them aware of the possibilities of abstinence oriented treatments and to avoid misunderstandings about the working mechanism and possible side effects of XRNT (e.g. some patients were afraid that XRNT is addictive as well).

In our study, treatment providers with a shorter career in addiction care are more willing to prescribe XRNT than their colleagues with a longer career in addiction care, but previous experience with oral naltrexone is not predictive of their willingness to prescribe XRNT, possibly because of mixed results with oral naltrexone. Many treatment providers state that XRNT should only be prescribed to patients who are highly motivated, who have adequate social support and who already have some (positive) experience with oral naltrexone. It is important that treatment providers inform the patients about the potential risks of XRNT (e.g. risk of heroin overdose, emergency pain management problems).

Our study has both strengths and limitations. Its main strength is the relatively large sample size of both patients and treatment providers. Another strength is that we asked the patients specifically whether they were interested in a new kind of treatment aimed at the complete cessation of heroin and methadone use (and not aimed at cessation of other drugs). However, our study also has some limitations. First, the questionnaires were only filled out by patients in addiction treatment centers in Amsterdam and Rotterdam and not in other cities in The Netherlands. Second, only patients in methadone maintenance or heroin-assisted treatment were approached, and no patients in abstinence oriented treatment. Third, we have no information on the total number of patients and treatment providers that were asked to participate and thus we have no information on the response rates of patients and treatment providers and no information about the representativeness of the study population. Fourth, we were only able to provide some, but not all, information to the patients about XRNT. A more detailed explanation during an interview might have produced different results. Fifth, the possibility of socially desirable answers by the patients cannot be excluded. Finally, abstinence may not be a suitable target for all drug users with a desire for abstinence. Failed attempts at abstinence may be more damaging and disappointing than successful harm-reduction treatment and harm-reduction treatment may be useful in the transition from drug use to abstinence (18).
In conclusion, the current study shows that many patients and the majority of treatment providers in methadone maintenance and heroine-assisted treatment programs in The Netherlands show interest in abstinence oriented treatments, including the prescription of extended-release naltrexone (XRNT) injections. It is therefore unfortunate that XRNT injections are still very costly and not reimbursed by the health insurance in The Netherlands.

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**Contributors**

Wim van den Brink, Anna E. Goudriaan, Jan Booij and Eline R. Zaaijer designed the study and wrote the protocol. Eline R. Zaaijer collected the data. Eline R. Zaaijer and Maarten W.J. Koeter conducted the statistical analysis. Eline R. Zaaijer wrote the first draft of the manuscript and all authors contributed to and have approved the final manuscript.

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