Chasing the Dragon Away: Personality as a protective factor and extended-release naltrexone as a treatment for heroin dependence
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Chapter 6

Summary and general discussion
Summary

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

Objectives
The main objectives of this thesis were (a) to gain better insight in the process of getting addicted to heroin in order to develop personality-based prevention strategies, by studying distinctive personality patterns in heroin users that became heroin dependent and heroin users that never became dependent; (b) to assess the interest of heroin dependent patients and their treatment providers in treatments directed at total abstinence and specifically in the treatment with extended-release naltrexone (XRNT); and (c) to study whether treatment with XRNT in heroin dependent patients results in decreased striatal dopamine transporter (DAT) availability and in anhedonia and depression as potential side-effects.

Chapter 1 provided a brief introduction to the epidemiology, the treatment situation and the pathophysiology of heroin dependence, its neurobiological aspects and XRNT treatment. The chapter ended with an outline of this thesis.

In Chapter 2 we compared personality traits of illicit opioid users who never became dependent (n=161) with personality traits of opioid dependent patients (n=402) and healthy controls (n=135) using the Temperament and Character Inventory (TCI, Cloninger, 1994) in order to better understand the potential protective role of personality in the development of opioid dependence in subjects who start to use illicit opioids. We found that never-dependent opioid users reported a strong need for social approval (high Reward Dependence) and high self-efficacy (high Self-Directedness), which may have protected them against becoming heroin dependent despite their tendency to seek novel and/or spiritual experiences and to avoid punishment (high Novelty Seeking, Self-Transcendence and Harm Avoidance, respectively), which, at least partly, may be the reason why they had started to use opioids. These results may be used in the development of prevention programs for young people with an increased risk for opioid use and dependence. Personalized interventions may be developed, based on a personality profile, similar to the successful interventions used by Conrod et al. in the prevention of alcohol and drug use (problems) (1,2).

In Chapter 3 we explored the support for abstinence oriented treatments and the acceptability of XRNT injections for heroin dependent patients in The Netherlands. We also studied the acceptability of XRNT injections among treatment providers. A total of 261 patients and 188 treatment providers filled out questionnaires, showing
that 58% of the patients wanted to become abstinent from all opioid agonists, 83% of which were interested in XRNT injections. Similarly, 81% of the treatment providers supported the prescription of XRNT to opioid dependent patients. Most of these patients were currently in an opioid agonist maintenance program and given these data it seems reasonable to regularly ask these patients about their treatment goal and not to automatically continue substitution treatment in these patients. In addition, we should investigate whether it would be possible to get XRNT available for patients in The Netherlands. There are some high quality studies (3–6) and one meta-analysis (7) indicating that XRNT is much more effective than oral naltrexone, and new initiatives should be taken to improve the access to XRNT for heroin dependent patients in The Netherlands.

However, among both patients and treatment providers, there are worries about the possibility of naltrexone-induced anhedonia and depression, because naltrexone blocks the μ-opioid receptor, which in turn may result in a decreased hedonic response to natural rewarding activities. This blockade of the μ-opioid receptor may indirectly cause a reduction of dopamine release and finally a down-regulation of striatal DATs. Therefore, we tested the hypothesis that treatment with (extended-release) naltrexone results in anhedonia and decreased striatal DAT availability. In Chapter 4 we report on a study in rats after 3 mg/kg short acting naltrexone for 10 days, and in Chapter 5 we present data on a study in humans two weeks after an intramuscular injection with 380 mg naltrexone using [123I]FP-CIT as a radiotracer for assessing DAT binding, using storage phosphor imaging in rats and Single-Photon Emission Computed Tomography (SPECT) imaging in humans. In rats, food intake, body weight gain and abdominal fatpad weight were studied as measures of anhedonia. In humans, we assessed symptoms of anhedonia and depression using self-report questionnaires. In both studies, no statistical significant effect of naltrexone treatment on striatal DAT availability was found, and there was also no effect of naltrexone on food intake in rats or on anhedonia in humans. This suggests that treatment with naltrexone has no negative effects on hedonic responses and that clinical use of naltrexone is compatible with a maintained pleasurable response to natural rewarding activities, at least in acute and subchronic treatment. Interestingly, we also showed that baseline striatal DAT binding (i.e., before the start of XRNT treatment) was significantly lower in opioid dependent patients than in matched controls, which is in agreement with previous studies (8–11), suggesting that chronic opioid use is associated with a decrease in striatal DAT availability. It is not clear whether this phenomenon represents a causal factor or a consequence of the disorder and we also do not know whether this low DAT availability is reversible.
General discussion

One of our main research questions was whether treatment with (extended-release) naltrexone causes anhedonia as a side-effect. This could be a logical consequence of the mechanism of action of naltrexone, which blocks the µ-opioid receptor, resulting in a reduced response to natural rewarding activities. In both our animal and our human study, we found, however, no evidence for anhedonia or depression during (extended-release) naltrexone treatment. In the human study we even found some improvement in depressive symptoms after XRNT treatment. Previous studies have indicated that anhedonia is related to reduced DAT availability. However, at baseline, we found no difference in Snaith-Hamilton Pleasure Scale (SHAPS) scores for anhedonia between patients and controls. Also, we found no decrease in striatal DAT availability and scores on the SHAPS for anhedonia during treatment with (extended-release) naltrexone. Importantly, a previous study by O’Brien et al. in alcohol dependent patients found that XRNT only inhibited the pleasure from drinking alcohol and not of other rewarding activities (12). We do not really understand the mechanism behind this the differential effect of naltrexone for different types of reward. A possible explanation for this selective reward suppressing effect of XRNT could be that patients do notice that using alcohol or opioids has become less rewarding, because they attribute excessive salience to alcohol or drugs, whereas they may not notice that daily activities and natural rewards have become less rewarding, because it is less important and less salient to them (13). However, Langleben et al. (2012) did find a suppressing effect of XRNT on reward from sugar intake in opioid dependent patients using the quantitative Sweet Taste Test (STT) (13). Therefore, more studies are needed aimed at understanding these mechanisms using different measures for the perception of reward. In addition, it may be of interest to compare µ-opioid receptor occupancy and subjective hedonic responses following natural rewards in abstinent opioid dependent patients with and without naltrexone on board.

Strengths and limitations

Several general limitations of our studies should be pointed out. Firstly, most of our studies were cross-sectional and thus it is impossible to make strong causal inferences based on these studies. For example, when we studied personality in different groups of opioid users in Chapter 2, it cannot be excluded that the duration of opioid use had an effect on personality characteristics and that we were looking at the consequences rather than the causes of heroin use or dependence. Secondly, in Chapters 4 and 5 we only measured striatal DATs. Therefore, it cannot be ruled out that (extended-release) naltrexone has a significant effect on the expression of postsynaptic dopamine receptors or dopamine release but not on striatal DATs. As we mentioned earlier, several recent studies have suggested
that, in heroin dependent patients, dopamine release per se does not play a role in the subjective, pleasurable effects of heroin (14,15) and that repeated heroin use may cause a blunted dopaminergic response (16). Also, dopamine $D_{2/3}$ receptor binding may be lower in heroin dependent patients than in controls (16). In future studies, it may be of interest to test whether treatment with XRNT could increase dopamine $D_{2/3}$ receptor density and/or dopamine release. Thirdly, in the human DAT imaging study using SPECT in Chapter 5, regions of interest were positioned on the caudate nucleus and putamen and DAT binding was thus mainly measured in the dorsal striatum. Due to resolution limitations, in our study it was not possible to determine ventral and dorsal DAT binding separately. However, in our animal study in Chapter 4 using phosphor imaging, DAT availability was measured in dorsal striatum and ventral striatum/nucleus accumbens separately, and no significant group differences were found between animals treated with naltrexone and animals treated with vehicle in either of the striatal subregions. Therefore, it is unlikely that the lack of effect in the human study is due to the fact that we were not able to adequately measure differences in the ventral striatum. Also, this study was not placebo-controlled. Fourthly, the treatment studies presented in Chapter 4 (rodents: short acting naltrexone for 10 days) and Chapter 5 (humans: XRNT for 2 weeks) were relatively short. Therefore, it cannot be excluded that if treatment would have been longer, we may have found differences in striatal DAT availability, in behavioral measures (rodents) and in questionnaire scores for anhedonia and depression (humans). However, studies that did find an effect of naltrexone on palatable food consumptions in rats (17–20) and human studies that did find an effect of naltrexone or naloxone on the rewarding effects of physical activity and sex (21,22), performed measurements already after a single dose of naltrexone. Similarly, Bhargava et al. (1996) found a decrease in DAT binding after only 7 days of treatment, i.e. quicker than our treatment durations (23). Furthermore, Baptista et al. (2000) found a decrease of food intake in rats after 21 days of naltrexone treatment, but only for high doses (above 4 mg/kg) (24). Therefore it is not very likely that our treatment duration of 10 days in rats and two weeks in humans was too short to induce changes in DAT availability or perceived anhedonia or depression. However, we cannot exclude that such changes would have occurred after a longer treatment period. Finally, it should be noted that we included only male rats and male heroin dependent patients and healthy controls in our studies. Therefore, we do not know whether the results of our studies are applicable to females. Previous studies have shown that DAT availability is higher in females than in males (25,26) and that females are more vulnerable to depressive symptoms (27). Thus, with more female subjects we could have expected higher DAT availability and higher Beck Depression Inventory (BDI) and SHAPS scores at baseline, both in heroin dependent patients and matched controls. Nevertheless, we expect that in female heroin dependent patients there would also be no changes in DAT availability and
SHAPS scores during naltrexone treatment. Future studies with both males and females are needed to confirm this assumption. However, the vast majority of heroin dependent patients worldwide is male (28), and our results are thus relevant for most heroin dependent patients treated with naltrexone.

**Clinical implications**

From Chapter 2 we concluded that there are certain personality traits that seem to be protective (high need for social approval and high self-efficacy) and other personality traits that seem to be risk factors (tendency to seek novel or or spiritual experiences and to avoid punishment) for the development of heroin dependence. This information can be used to develop screening strategies to detect adolescents with an increased risk for opioid use and dependence. Furthermore, the (conceptual and empirical) distinction between personality (disorders) and developmental disorders like attention-deficit/hyperactivity disorder (ADHD) and conduct disorders (CD) is not always clear and the current findings seem to coincide with findings showing an increased risk of drug addiction in children with ADHD and/or CD (29). A published meta-analysis found no effect of school programs aimed at reducing first drug use and preventing children from becoming addicted in case they experiment with drugs (30). Therefore, universal prevention does not seem the most productive strategy and other strategies, including selective and indicated preventions are needed. For example, TCI profiles may be used in selective prevention programs that provide personality-targeted interventions. A study by Conrod et al. showed that selective, short personality-targeted interventions can prevent the onset of substance abuse in adolescents who are at high risk (1). Similarly, selective drug prevention programs can be designed directed at youngsters with ADHD and/or CD. Studies on the preventive effect of stimulant treatment of children with ADHD are inconclusive (31), but a recent study from The Netherlands shows great promise in this respect (32).

In The Netherlands, the current guideline on opioid addiction recommends maintenance treatment with methadone (opioid receptor agonist) or buprenorphine (partial opioid receptor agonist) as the first line intervention in heroin dependent patients because of its strong evidence base (33). However, from Chapter 3 we concluded that many heroin dependent patients in (partial) agonist maintenance treatment are interested in total abstinence of all opioids and treatment with XRNT injections. Moreover, XRNT has repeatedly shown to be an effective treatment, especially compared to oral, immediate-release naltrexone (6). Therefore, it should be considered not to automatically start and continue opioid substitution treatment. On the other hand, one should be careful not to disrupt a patient’s stable and fulfilling life when successfully treated with opioid substitution (34). In accordance with the Dutch guideline (33), abstinence oriented treatments should only be considered in the case of stable motivation, absence of active comorbid psychiatric disorders and
social stability. For a full personal recovery it is not enough to just reach abstinence, it is also important to be able to live a fulfilling, hopeful and contributing life (35).

In addition to the professional and patient perspective there are also public health perspectives, including cost and cost-effectiveness aspects of the treatment of patients with heroin dependence. In a recent study by Baser et al. (36), performed in the USA, using a retrospective claims database analysis, total healthcare costs of treatment with methadone, buprenorphine, oral naltrexone and XRNT in opioid dependent patients were compared. They showed that patients receiving one of these pharmacotherapies had fewer inpatient admissions and lower total healthcare cost compared to patients who were not treated with medication. Patients treated with XRNT had fewer inpatient admissions and total healthcare costs were not significantly different from those of the patients treated with oral naltrexone or buprenorphine. The total costs for XRNT treatment were even 50% lower than those for methadone treatment, in spite of the higher medication costs for XRNT per se. Also a recent study by Jackson et al. (37) estimating cost effectiveness of XRNT compared to treatment with methadone and buprenorphine showed that XRNT is cost effective. However, while XRNT proved to be more effective than both methadone and buprenorphine, it also proved to be more costly (extra costs per opioid-free day compared to methadone, the next-most effective treatment, were $72). Together with our data on the acceptability of XRNT by patients and treatment providers, these results support new initiatives to make XRNT available and affordable for patients in The Netherlands.

Future research
In Chapter 4 we compared rats that were treated with short acting naltrexone for 10 days to rats that were treated with vehicle on striatal DAT availability, food intake and body weight gain. In future studies, rats should be treated with (extended-release) naltrexone for more than 10 days to exclude the possibility that effects take place after the treatment period that we used (subchronic vs. chronic treatment). Secondly, studies should also include rats that are pre-treated with heroin or heroin addicted animals, because (chronic) heroin use may result in internalization, sensitization or desensitization of opioid receptors (38) and/or in reduced DAT availability (8,9,11,39). This is important, because in our human study we found reduced DAT availability in abstinent heroin dependent patients compared to healthy controls at baseline. Thirdly, in our animal study we measured cumulative chow intake, body weight gain and abdominal fatpad weight as measures of anhedonia. Chow intake is, however, not an ideal measure of anhedonia or reward, because it may be driven metabolic needs. Intake of a palatable diet may be a better measurement for future animal studies on the effects of naltrexone on hedonic response. For our study in Chapter 4 we could not use a palatable diet, because the diet itself would have induced weight gain and increased abdominal fat mass, which would
have altered dopamine signaling (40,41), and thus would make interpretation more difficult. For future studies, a sucrose preference test, where animals can choose between a bottle of 1% sucrose solution or tap water following a period of food and water deprivation, might be a better measure for anhedonia (42). Fourthly, future studies should directly compare the effects of short acting naltrexone to XRNT. When using the extended-release form, the total naltrexone dose can be much lower, because it avoids the first-pass metabolism of the liver (43), so possibly also fewer side-effects can be expected. Finally, it would be very interesting to study the effect of naltrexone on both the opioid and the dopamine system using in vivo positron emission tomography (PET) imaging and ex vivo imaging (phosphor imaging) in rats, and PET imaging in humans, since PET tracers to image the opioid system are now available (44).

Previous research has shown that genetic variation in the μ-opioid receptor (OPRM1) is related to treatment success with naltrexone in alcohol dependent patients (45,46). Variation in OPRM1 seems to modify the effect of naltrexone (47). Therefore, using genetic information in treatment decisions may also be suitable in the case of opioid dependent patients and help to provide them with an individual treatment plan. This has not been studied yet.

For future research it may also be interesting to compare a treatment with (extended-release) naltrexone to a treatment with (extended-release) nalmefene (48,49). Apart from being a μ-opioid receptor antagonist, nalmefene is also a partial κ-opioid receptor agonist. Like in alcohol dependence (50), rodent studies have shown that heroin dependence is associated with increased κ-opioid receptor activation, which in turn may lead to persistent heroin use that is at least partly due to dysphoria associated with κ-opioid receptor activation (51). Moreover, many heroin dependent patients suffer from depression and dysphoria. In a situation of κ-opioid receptor hyperactivity, the introduction of a partial κ-opioid receptor agonist may act as a functional antagonist and reduce the risk of drug use and dysphoria. As such, nalmefene may have some benefits over naltrexone in the treatment of patients with chronic heroin dependence. However, currently there are no data available on the comparative effectiveness of naltrexone and nalmefene in heroin dependent patients. Finally, we would like to note that in contrast to naltrexone, nalmefene is not hepatotoxic, so during treatment with nalmefene liver function testing is not needed. On the other hand, hepatotoxicity is rarely seen in patients treated with a standard dose of naltrexone (50 mg/day). Therefore, this is probably only a small advantage of nalmefene over naltrexone (52).

In future studies on the effects and side effects of different opioid receptor antagonists in heroin dependence (oral naltrexone, XRNT, nalmefene) it seems useful to employ functional Magnetic Resonance Imaging (fMRI). A recent fMRI study by Langleben et al. (53), in which heroin-related and neutral images were shown, suggests that XRNT decreases brain responses to drug cues with a clear
dose-response relationship in heroin dependent patients. For future studies it will be interesting to also show images of natural rewarding situations or activities (e.g. images of food and sex) to assess whether (extended-release) naltrexone influences only drug-related brain responses or hedonic brain responses in general. Structural imaging can also add valuable information about striatal volume. This is important, because in the analysis of our SPECT study we used a template with fixed region of interests (ROIs) for the caudate nucleus, putamen and occipital cortex. In the case of decreased striatal volume due to XRNT treatment, we would underestimate striatal DAT availability in this region. Previous MRI studies using volume measurements found that anhedonia was associated with decreased volumes of nucleus accumbens (54,55) and the anterior caudate region (55). Depression was associated with reduced volumes in caudate nucleus and putamen (56). Therefore, it would be interesting to study striatal volume before and during naltrexone treatment.

WHO guidelines advise to add psychosocial treatment to XRNT, because it provides the patient with skills to develop healthy behavior while protected against relapse into opioid use (4,57). Examples of psychosocial interventions are psychotherapy, counseling and self-help groups. However, the added value of such intervention have not been studied yet (57).

XRNT is also effective in other patient groups. It showed to be effective in alcohol dependent patients, in which it increased abstinence and attenuated alcohol-related cues. There might even be a role for XRNT in the treatment of patients with stimulant dependence (58,59), but this requires further studies (43).

Conclusions

From this thesis, it can be concluded (a) that there are distinctive personality traits that form a risk for or protect against heroin use and heroin dependence that may be used for the development of personality-targeted personalized interventions; (b) that many patients are interested in becoming fully abstinent and in treatment with XRNT; (c) that treatment with (extended-release) naltrexone seems to have no significant effect on striatal DAT availability and is not associated with a reduced pleasurable response to natural rewarding activities (anhedonia).
Summary and general discussion

References


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