Chapter 1

General introduction and outline of the thesis
General introduction

Heroin dependence

Heroin dependence is a chronic, relapsing disorder characterized by compulsive heroin use despite harmful consequences, loss of control resulting in the inability to reduce or to stop illicit heroin use, and the development of negative emotions (e.g. dysphoria, anxiety, irritability) when there is no heroin available (1).

Opioid dependence causes severe problems for patients and their family members and imposes an enormous economic burden on society (2,3). Worldwide, opioid dependence is one of the most common illicit drug dependencies (together with cannabis, cocaine and amphetamine dependence) with a mean estimated prevalence of 0.22% (2). The majority of patients are male (70%). In Australia, the United States and Canada, the estimated prevalence of problematic opioid use is 0.63%, 0.58% and 0.30%, respectively (4). In Europe, the estimated prevalence of problematic opioid use among adults (15-64 years) is 0.42% (range 0.10% - 0.80%) and the main illicit opioid that is used is heroin. Most of the opioid use in Europe occurs in urban areas among marginalized populations. There have been two waves of increasing heroin use in Europe: one starting in the mid-1970s and another one in the mid to late 1990s. Countries with the highest prevalence of heroin dependence in Europe are the United Kingdom, Latvia, Malta and Luxembourg. Countries with the lowest prevalence are Turkey, Hungary, Poland and The Netherlands (5). In The Netherlands (10.5 million inhabitants in the age range of 20-65 years), there are about 14,000 problematic opioid users (0.13%) (6). Heroin can be inhaled, snorted or injected (5). In The Netherlands, currently heroin is mainly used by inhalation (>90%), i.e. ‘chasing the dragon’ (7,8). This term is used on the streets, and refers to chasing the ‘dragon’s tail’ of smoke with a straw, after vaporizing the heroin by heating it carefully on aluminum foil (8).

However, not all people that once tried heroin became addicted. Many people have tried heroin and yet most did not become addicted. This is an intriguing phenomenon and little is known about the factors that prevent certain people who started to use heroin from becoming addicted to it. Personality traits have been associated with the risk for becoming opioid dependent (9). Opioid dependent people score significantly higher than healthy controls on Novelty Seeking (9), Harm Avoidance and Self-Transcendence, and significantly lower on Reward Dependence, Self-Directedness and Cooperativeness (10). However, nothing is known about the personality traits of people who used heroin, but never became dependent to it. In this thesis, we use the Cloninger’s Temperament and Character Inventory (TCI) to study personality factors in relation to both the unproblematic and the problematic use of heroin (11). In order to assess the possible protective role of personality, we will also study illicit opioid users who never became opioid dependent.
Nevertheless, many heroin users did become opioid dependent. In The Netherlands there are currently about 14,000 problematic heroin users and 10,000 of them (71%) are in contact with the treatment system (12). The majority of these patients are treated with methadone, buprenorphine or pharmaceutical heroin directed at reduced illicit opioid use and improvement of functioning and quality of life. Only a minority is treated in abstinence oriented programs with or without pharmacological support of an opioid receptor antagonist such as naltrexone (12). However, a worldwide move towards recovery-oriented treatments is taking place with more emphasis on total abstinence of all opioids. This change in orientation is also taking place in The Netherlands with an increased interest in total abstinence, the use of opioid receptor antagonists (naltrexone) to support abstinence and the intention to reach full personal recovery (13,14). However, very little is known about the support for abstinence oriented treatments in patients and treatment providers and even less is known about the acceptability of naltrexone injections as one possibility to reach stable abstinence of all opioids. This is important, because there are serious doubts about the effectiveness of oral naltrexone. At the same time, some studies suggest that extended-release naltrexone (intramuscular injections or subcutaneous implants) is more effective than oral naltrexone, mainly due to the better long-term compliance (15,16). However, there are also indications that (extended-release) naltrexone might be associated with anhedonia and depression (17), side effects that may seriously hamper full personal recovery. In this thesis, we study the interest and acceptability in intramuscular extended-release naltrexone injections in patients and treatment providers in methadone, buprenorphine and heroin maintenance programs in The Netherlands. In addition, we study the risk of anhedonia and depression in rodents and humans treated with (extended-release) naltrexone.

Neurobiological aspects of heroin dependence

After intravenous injection or inhalation, heroin (diacetylmorphine) almost immediately enters the brain, and is converted there into its main active metabolites: morphine and 6-monoacetylmorphine (6-MAM) (18). By binding to the μ-opioid receptor, heroin induces its well-known euphoric effects (19).

In addition, animal studies have suggested that dopamine release in the nucleus accumbens plays an important role in compulsive drug seeking behaviors in general and more specifically in compulsive heroin (self-)administration (20–22). In addition, administration of dopamine receptor antagonists have been shown to interfere with the development of these heroin drug seeking behaviors in rodents (23–25). Unlike stimulants like dexamphetamine, the effect of heroin on the dopamine system is indirect. Animal studies have shown that active heroin metabolites induce dopamine release by decreasing the inhibitory activity of gamma-aminobutyric acid (GABA) neurons on the dopamine neurons in the ventral tegmental area (18). It has also been found that, after release, dopamine binds to pre- and postsynaptic dopaminergic
receptors and that stimulation of the postsynaptic dopamine receptors may cause the motivational effects of heroin (18,26). In line with this, heroin cue-exposure and heroin craving have been reported to be associated with increased dopamine release in the right putamen in abstinent opioid-dependent patients (27). Dopamine release also plays an important role in the rewarding effects of other substances of abuse; stimulants (28), nicotine (29) and alcohol (30). Therefore, a role of dopamine release in the effects of heroin seems logical. However, several recent studies have suggested that dopamine release per se does not play a role in the euphoric effects of heroin, in heroin self-administration and in the anticipation of heroin reward. For example, a recent human study, in methadone-maintained patients, did not find an increase in dopamine release after use of opioids, while patients did feel a ‘high’ (31). In addition, an animal study in which a dopamine D1 receptor antagonist was administered in the nucleus accumbens did not reduce self-administration of heroin (24). Finally, a study in methadone-maintained patients has shown that striatal dopamine release did not increase the anticipation of heroin reward (32). These unexpected findings may result from differences between the studies in the duration of the dependence, the current state of substance use (actively using, in opioid maintenance treatment or abstinent) or the (neuroimaging) techniques used and subjects that were studied, e.g. heroin may induce dopamine release in non-dependent animals and healthy volunteers, whereas dopamine release may be blunted in chronic heroin-dependent patients. Indeed, while the stimulant dexamphetamine is able to induce striatal dopamine release in healthy controls, this effect is blunted in recreational dexamphetamine users, cocaine dependent and heroin dependent patients (33–35). Nevertheless, although not all results are consistent, several studies have suggested that repeated heroin use induces changes in the dopamine system, e.g. a blunted dopaminergic response (33–35). In addition, e.g. abstinent opioid-dependent patients showed lower dopamine transporter (DAT) availability compared to healthy controls (36–39). Thus, both the opioid and the dopamine system seem to play a role in the rewarding effects of heroin.

Extended-release naltrexone
Naltrexone is a competitive µ-opioid receptor antagonist that is used in opioid dependent patients as part of abstinence-oriented treatment to prevent relapse after detoxification. It blocks the µ-opioid receptor to prevent heroin from having a direct euphoric effect. However, in randomized controlled trials, oral naltrexone treatment is not better in producing sustained abstinence than placebo, mainly because of poor treatment compliance (40). Extended-release naltrexone formulations (XRNT) were developed to overcome this poor compliance (41). Meanwhile, both naltrexone implants (42) and injections (41) have shown to be effective clinically. In opioid dependent patients, naltrexone injections improve treatment retention, reduce craving, and prevent relapse (16,43).
There are, however, concerns about blocking opioid receptors with (extended-release) naltrexone, because opioid receptors are also directly involved in hedonic responses to natural rewarding behaviors (17). In response to natural rewarding activities, such as eating and sex, endogenous opioids are released that bind to the µ-opioid receptor (44). As mentioned earlier, via this mechanism, dopamine release may be induced (depending on the a priori condition; see earlier), by decreasing the inhibitory activity on dopamine release of GABA-ergic neurons, and thereby produces motivational effects. So, at least theoretically, when µ-opioid receptors are blocked by naltrexone, this may lead to a decrease in dopamine release in response to natural rewarding activities (i.e. anhedonia).

After its binding to the postsynaptic dopamine receptors, dopamine is degraded or transported back into the presynaptic dopaminergic neuron via the DAT. Thus, the DAT removes dopamine from the synapse, and thereby controls the dopamine levels in the synapse. In response to chronic changes in dopamine release, and thereby changes in dopamine levels in the synapse, DAT expression will change (45,46). Indeed, studies have shown that chronic naltrexone administration results in decreased striatal DAT availability (47) probably as a compensatory response to the (chronically) decreased dopamine levels in the synaptic cleft. Interestingly, human studies have also shown that anhedonia and apathy are associated with decreased DAT availability (48,49). Therefore, we hypothesize that (extended-release) naltrexone may affect DAT expression and thereby may cause depression and anhedonia. However, previous human studies using self-report questionnaires have shown inconsistent results regarding use of naltrexone and the occurrence of anhedonia (50–53). Therefore, more knowledge about these potential side-effects is needed for patients and their treatment providers using both self-report questionnaires and biological indicators of such side effects, including a possible reduction in striatal DAT availability. Striatal DAT availability can be measured with several techniques, including storage phosphor imaging in animals ex-vivo (54), and with Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) in living animals and humans (55).

**Objective and outline of this thesis**

The first study in this thesis (Chapter 2) includes heroin dependent patients, heroin users that never became dependent and healthy controls that never used heroin to assess both protective and risk factors for heroin use and the development of heroin dependence. The emphasis in this study is on personality as one of the most important factors. This knowledge is important for a better understanding of the addiction process and for the planning of future prevention strategies that may need to be tailored to specific personality factors (56,57).
Internationally there is a renewed interest in personal recovery and related to that the abstinence oriented treatment of opioid dependent patients with or without the pharmacological support of (extended-release) naltrexone. XRNT injections are already registered in the United States and Russia, but not in most other European countries, including The Netherlands. Chapter 3 explores the need for abstinence oriented treatments among patients and the acceptability of naltrexone injections by these patients and their treatment providers using a self-report survey.

There are, however, concerns that blocking opioid receptors with (extended-release) naltrexone leads to less pleasure from natural rewarding daily activities (i.e. anhedonia and depression). Therefore, one of the major aims of this thesis was to study whether treatment with (extended-release) naltrexone affects striatal DAT availability and pleasure from natural rewarding activities. This was studied both in animals (Chapter 4) and in humans (Chapter 5), using the same radioligand, $[^{123}]$FP-CIT, to assess ex vivo and in vivo striatal DAT occupancy by naltrexone, respectively.
References

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