Chasing the Dragon Away: Personality as a protective factor and extended-release naltrexone as a treatment for heroin dependence
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Chapter 2

Personality as a risk factor for illicit opioid use and a protective factor for illicit opioid dependence

Eline R. Zaaïjer, Jessica Bruijel, Peter Blanken, Vincent Hendriks, Maarten W.J. Koeter, Mary Jeanne Kreek, Jan Booij, Anna E. Goudriaan, Jan M. van Ree, Wim van den Brink

Abstract

Background: Most studies investigating the role of personality as a risk factor for the development of opioid dependence compare dependent opioid users with healthy controls who never used heroin. In order to understand the potential protective role of personality, it is crucial to compare illicit opioid users who never became dependent with dependent opioid users.

Aims: This study aims to examine the role of personality as a risk factor for opioid use and as a protective factor for the development of opioid dependence.

Methods: Comparing personality factors between three groups: (1) 161 never-dependent illicit opioid users who have been using illicit opioids but never became opioid dependent; (2) 402 dependent opioid users in methadone maintenance treatment or heroin-assisted treatment; and (3) 135 healthy controls who never used heroin. Personality was assessed with a short version of Cloninger’s Temperament and Character Inventory.

Results: Never-dependent opioid users reported more Novelty Seeking and Harm Avoidance and less Self-Directedness and Cooperativeness than healthy controls and more Reward Dependence and Self-Directedness, and less Harm Avoidance than dependent opioid users. Furthermore, never-dependent opioid users reported more Self-Transcendence than both dependent opioid users and healthy controls.

Conclusions: Never-dependent opioid users may have started to use opioids partly due to their tendency to seek novel and/or spiritual experiences (high Novelty Seeking, high Self-Transcendence) and their tendency to avoid aversive stimuli (high Harm Avoidance), whereas they may have been protected against the development of dependence by their need for social approval (high Reward Dependence) and their self-efficacy (high Self-Directedness).

Keywords: Personality, Opioid, Dependence, TCI, Risk factors, Protective factors
1. Introduction

Opioid dependence is a worldwide health problem with severe medical and social consequences (1). In The Netherlands, the estimated number of problematic heroin users amounts to 18,000 (2), of which almost 13,000 (72%) are registered in addiction treatment services: 60% in methadone and buprenorphine maintenance treatment, 5% in heroin-assisted treatment (medical prescription of diacetylmorphine), and 7% in abstinence oriented treatments. Most of these interventions are proven effective and both morbidity and mortality have been reduced resulting in an increasing life time expectancy of opioid addicts in The Netherlands (3).

However, many more people have tried heroin and very little is known about the factors that protect heroin users from becoming heroin dependent. The current study attempts to fill this gap with special emphasis on the role of personality as a potential protective factor for the development of opioid dependence in subjects with a life-time history of self-exposure to illicit opioids.

Personality traits such as impulsivity have been associated with continued use, relapse, and unfavourable treatment outcomes in several substance use disorders, including opioid dependence (4), cocaine dependence (5,6), and alcohol dependence (7–10). Cloninger’s Temperament and Character Inventory (TCI) has been frequently used in these studies and several of those studies have shown that opioid dependent patients score significantly higher on Novelty Seeking (NS) than healthy controls (11–16). Novelty Seeking is also associated with an increased risk of early drug experimentation, which is consequently associated with an increased risk of dependence later in life (11). Opioid dependent patients also score higher on Harm Avoidance (HA; (13–16)). Opioid use may function as a self-medication strategy to control anxiety and to overcome feelings of inadequacy (15), which could explain the association between high anxiety personality traits and opioid dependence. Lower Self-Directedness (SD) is an element of an immature personality profile, which is often found in addicts (13,16). Self-Directedness and sometimes also Cooperativeness (C) and Reward Dependence (RD) were reported to be significantly lower in opioid dependent patients compared to healthy controls (11,13,14). Higher Reward Dependence is an indication of increased sensitivity to social approval and social rewards (14), and low Reward Dependence thus makes it is easier to use illegal drugs (11). However, Fassino et al. (13) found that Reward Dependence was only significantly lower in heroin addicts when they also had a personality disorder. Previous studies did not show a difference in Persistence (P) between opioid dependent patients and healthy controls. Finally, Korf et al. (17) found that the never-dependent opioid users in this study had a non-conventional life style and most of them were alternative or artistic, traits that are associated with high Self-Transcendence (ST). Finally, previous studies have reported that opioid dependent people score significantly higher on Self-Transcendence than healthy controls (11,13,14).
In most of these studies, opioid dependent patients were compared with healthy–opioid-naïve–controls or different opioid dependent groups were compared with each other. Unfortunately, there are no studies comparing the personality characteristics of opioid dependent patients with those of illicit opioid users who never became dependent. Such data could be very important for a better insight in the risk factors and underlying processes responsible for the development of heroin dependence and the prevention and early treatment of dependence.

Therefore, the aim of this study is to identify personality traits associated with the development of illicit never-dependent opioid use and the protection against dependence in never-dependent opioid users by comparing opioid users who never became opioid dependent (NDO), dependent opioid users (DO), and healthy controls without any substance use disorder who never used illicit opioids (HC).

Based on the above summary of the literature, and assuming that never-dependent opioid users have TCI scores between those of dependent opioid users and healthy controls, we test the following hypotheses: (1) never-dependent opioid users score lower on Novelty Seeking and Harm Avoidance, and higher on Reward Dependence, Self-Directedness and Cooperativeness compared to dependent opioid users; (2) never-dependent opioid users score higher on Novelty Seeking and Self-Transcendence compared to healthy controls; (3) dependent opioid users score higher on Novelty Seeking, Harm Avoidance and Self-Transcendence and lower on Reward Dependence, Self-Directedness and Cooperativeness compared to healthy controls, and there will be no difference on Persistence between dependent opioid users and healthy controls.

2. Methods

This study is part of the ongoing research project “Opioid Receptors and Addiction: a Genetic Approach.” The primary objective of the project is to determine risk and protective factors for the development of opioid dependence, including genetic polymorphisms, family history of mental disorders and personality. This report concerns the role of personality in the risk of never-dependent illicit opioid use and the protection against the development of illicit opioid dependence.

2.1. Subjects

Three different samples were recruited, including a total of 698 participants (Table 1):

2.2. Group 1. Never-dependent illicit opioid users (NDO)

Subjects in this group (N=161) had to demonstrate a lifetime history of self-exposure to illicit opioids, as indicated by at least five and a maximum of 100 opioid self-administrations. To minimise the possibility that these participants would become opioid dependent after entering the study, first opioid use should have taken place
at least 2 years before entering the study. These participants were recruited through “convenience” sampling, like advertisements in local media, as well as through “snowball” or “chain referral” sampling (17). About one third (32%) of these participants had taken illicit opioids 5–9 times, about half (52.6%) had taken them 10–49 times, and the rest (16%) had taken illicit opioids more frequently. The vast majority (87%) had experience with illicit heroin, more than half (57%) with opium and 43% had used both substances (17). Unfortunately we have no information on the route of administration.

2.3. Group 2. Dependent opioid users in methadone maintenance or heroin-assisted treatment (DO)

Subjects in this group (N=402) had to be DSM-IV opioid dependent for at least 5 years. They were recruited from methadone maintenance programs (N=200) and heroin-assisted treatment programs (N=202) in The Netherlands (18–20). In the Netherlands, the route of administration of street heroin is mainly (90–95%) through inhalation of heroin vapors (chasing the dragon) and intravenous use occurs in only 5-10% of all subjects (2). Similar heroin consumption patterns are seen in the Dutch treatment settings, including methadone maintenance treatment and heroin assisted treatment programs (2,20). These two subgroups did not differ on any of the TCI-105 subscales and were therefore treated as one group in all analyses.

2.4. Group 3. Healthy controls (HC)

Subjects in this group (N=135) had no history of any illicit opioid use and no history of alcohol or drug (including cannabis) dependence (DSM-IV). Nicotine dependence was not an exclusion criterion. They were recruited in The Netherlands through “convenience” sampling, like advertisements in local media, personal contact, or referral by others.
All participants had to be at least 25 years of age. The study was approved by the Central Committee on Research Involving Human Subjects (CCMO) in the Netherlands (protocol number P04.0156C) and all participants gave written informed consent.

2.5. Assessment
Socio-demographic characteristics: Information about age, gender, country of origin, education and marital status was collected using a standard questionnaire. Ethnicity was operationalized as follows: a subject was considered Caucasian when both parents originated from a European country or the USA and non-Caucasian otherwise. The latter group comprised mainly of subjects with parents from Asian countries, Surinam, Middle Eastern or Hispanic countries.

Diagnosis: The SUD section of the computerized fully structured Composite International Diagnostic Interview (CIDI Auto 2.0; (21)) was used to obtain DSM-IV substance dependence diagnoses. The CIDI can be used by non-clinicians and has good reliability and validity when compared to semi-structured interviews such as the AUDADIS and the SCAN (22).

Personality and personality disorder: Cloninger’s Temperament and Character Inventory (TCI; (23)) was used as the main personality questionnaire in the study. The TCI is a self-report, yes-or-no type questionnaire, designed to quantify individual differences on four temperament and three character dimensions. A validated Dutch translation of the TCI is available, including a shortened version (TCI-105), in which the original 240 items are reduced to 105 items with 15 items per scale. With the TCI-105, all seven dimensions of the TCI are measured: Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD), Persistence (P), Self-Directedness (SD), Cooperativeness (C) and Self-Transcendence (ST).

2.6. Statistical analyses
Single imputation (mean imputation) was used for missing items on the TCI. This was performed for each scale by replacing the missing value with the mean score of the non-missing items of the person for the specific scale.

To determine whether groups significantly differed on socio-demographic characteristics, one-way ANOVA and Chi-square tests were used for continuous and categorical variables, respectively.

A MANCOVA was performed with the seven scales as dependent variables, group as an independent factor, gender, education (‘medium secondary school or higher’) and ethnicity (‘Caucasian’) as co-factors and age as a covariate. All covariates fulfilled the parallel slope assumption. When the multivariate test was significant, univariate ANCOVAs were used to determine which scales significantly differed between groups. Post-hoc tests were used to compare the groups for each dependent variable where ANCOVAs showed significant group differences. To adjust for multiple
testing, statistical significance was defined as \( p < 0.0024 \) (Bonferroni correction for three groups and seven TCI scales: \( \alpha = 0.05/21 = 0.0024 \)).

All statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) version 20.

3. Results

3.1. Sample characteristics
Socio-demographic characteristics and opioid use of the three groups are presented in Table 1. The groups differed significantly on several socio-demographic and opioid use characteristics. The DO group was older, contained more males and less Caucasians and a lower level of education compared to the NDO and the HC groups. The percentage of married and cohabiting persons was higher in the HC group than in the NDO and DO groups. In addition, we found a small but significant difference in the age of onset of first opioid use between the DO and the NDO groups.

3.2. Temperament and character inventory
Internal consistency of the TCI-105 subscales was very similar for all three groups and generally good to excellent with Cronbach's \( \alpha \) ranging from 0.533 for Cooperativeness in the HC group to 0.895 for Self-Transcendence in the NDO group. The TCI-105 scores of the HC group fell within the norm scores of the Dutch population (data not presented).

In the MANOVA, we found a significant multivariate effect of group on the TCI-105 scales, Pillai's Trace, \( V = 0.4, F(14, 1382) = 24.7, p = < 0.001 \). The seven ANCOVA's showed no significant group by sex, group by education, group by age and group by ethnicity interactions on the TCI-105 scales. Results of univariate ANCOVAs and post hoc tests are given in Tables 2 and 3. Within the NDO group there were participants with (\( N = 99 \)) and without (\( N = 65 \)) a lifetime DSM-IV substance use disorder diagnosis other than opioid dependence. However, these two subgroups did not differ on any of the TCI-105 subscales, and therefore the NDO-group was treated as one group in all analyses.

3.3. Group comparisons
Never-dependent opioid users vs. dependent opioid users: Compared to dependent opioid users, never-dependent opioid users scored significantly lower on Harm Avoidance (conform hypothesis) and higher on Reward Dependence and Self-Directedness (both conform hypotheses) and Self-Transcendence. No significant differences in Novelty Seeking (not conform hypothesis) and Persistence scores were found between these groups (Table 3).

Never-dependent opioid users vs. healthy controls: Compared to healthy controls, never-dependent opioid users scored significantly higher on Novelty Seeking, Harm
Avoidance and Self-Transcendence (all three conform hypothesis) and significantly lower on Self-Directedness and Cooperativeness. No significant differences in Reward Dependence and Persistence scores were found between these groups (Table 3).

Dependent opioid users vs. healthy controls: Compared to healthy controls, dependent opioid users scored significantly higher on Harm Avoidance and Self-Transcendence (both conform hypotheses) and significantly lower on Reward Dependence, Self-Directedness and Cooperativeness (all three conform hypotheses). No significant Novelty Seeking scores were found between these groups (not conform hypothesis; Table 3).

### Table 2. TCI-105 scores of never-dependent opioid users (NDO), dependent opioid users (DO) and healthy controls (HC), ANCOVAs and post hoc tests.

<table>
<thead>
<tr>
<th></th>
<th>NDO 161</th>
<th>DO 402</th>
<th>HC 135</th>
<th>F (2, 691)</th>
<th>P</th>
<th>Pairwise comparisons between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novelty Seeking</td>
<td>8.6 (3.0)</td>
<td>7.8 (2.7)</td>
<td>7.3 (2.9)</td>
<td>7.4</td>
<td>&lt;0.001</td>
<td>NDO &gt; HC</td>
</tr>
<tr>
<td>Harm Avoidance</td>
<td>5.6 (3.7)</td>
<td>7.7 (3.8)</td>
<td>4.1 (3.3)</td>
<td>49.1</td>
<td>&lt;0.001</td>
<td>DO &gt; NDO &gt; HC</td>
</tr>
<tr>
<td>Reward Dependence</td>
<td>9.4 (2.8)</td>
<td>8.2 (2.7)</td>
<td>9.7 (2.6)</td>
<td>13.1</td>
<td>&lt;0.001</td>
<td>HC, NDO &gt; DO</td>
</tr>
<tr>
<td>Persistence</td>
<td>8.3 (3.4)</td>
<td>7.8 (3.0)</td>
<td>8.6 (2.5)</td>
<td>4.4</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>Self-Directedness</td>
<td>11.5 (3.2)</td>
<td>9.3 (3.6)</td>
<td>13.8 (1.9)</td>
<td>70.1</td>
<td>&lt;0.001</td>
<td>HC &gt; NDO &gt; DO</td>
</tr>
<tr>
<td>Cooperativeness</td>
<td>12.4 (2.6)</td>
<td>11.5 (2.7)</td>
<td>13.9 (1.4)</td>
<td>28.7</td>
<td>&lt;0.001</td>
<td>HC &gt; NDO, DO</td>
</tr>
<tr>
<td>Self-Transcendence</td>
<td>7.4 (4.6)</td>
<td>5.7 (4.2)</td>
<td>3.2 (3.3)</td>
<td>38.7</td>
<td>&lt;0.001</td>
<td>NDO &gt; DO &gt; HC</td>
</tr>
</tbody>
</table>

Means represent raw data that were not adjusted for gender, education, ethnicity and age (SD). Seventy of the 698 subjects (13 NDO, 47 DO, 10 HC) had missing items on the TCI-105 (1-9 items), but none of the participants missed four or more questions from one scale.

### Table 3. Standardized effect sizes (Cohen’s $d$) for significant ($p<0.0024$) differences in TCI-105 scores between never-dependent opioid users (NDO), dependent opioid users (DO) and healthy controls (HC).

<table>
<thead>
<tr>
<th></th>
<th>NDO/DO</th>
<th>NDO/HC</th>
<th>DO/HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novelty Seeking</td>
<td>NS</td>
<td>0.42</td>
<td>NS</td>
</tr>
<tr>
<td>Harm Avoidance</td>
<td>-0.58</td>
<td>0.49</td>
<td>1.07</td>
</tr>
<tr>
<td>Reward Dependence</td>
<td>0.42</td>
<td>NS</td>
<td>-0.51</td>
</tr>
<tr>
<td>Persistence</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Self-Directedness</td>
<td>0.55</td>
<td>-0.86</td>
<td>-1.30</td>
</tr>
<tr>
<td>Cooperativeness</td>
<td>NS</td>
<td>-0.65</td>
<td>-0.86</td>
</tr>
<tr>
<td>Self-Transcendence</td>
<td>0.47</td>
<td>1.05</td>
<td>0.56</td>
</tr>
</tbody>
</table>
4. Discussion

The present study compared personality factors in three groups: illicit opioid users who never became dependent, opioid dependent patients in methadone maintenance or heroin-assisted treatment and healthy controls who never used illicit opioids.

Confirming most of our hypotheses, never-dependent opioid users reported more Novelty Seeking and Harm Avoidance and less Self-Directedness and Cooperativeness than healthy controls and more Reward Dependence and Self-Directedness, and less Harm Avoidance than dependent opioid users. Furthermore, never-dependent opioid users reported more Self-Transcendence than both dependent opioid users and healthy controls.

The higher level of Reward Dependence in never-dependent compared to dependent illicit opioid users means that never-dependent illicit opioid users were more sensitive to social approval (14) and this may have protected them against developing dependence. In contrast, persons with low Reward Dependence who experiment with illegal use may be less influenced by the social disapproval of their illegal drug use (11). In addition, the higher level of Self-Directedness in never-dependent illicit opioid users may have helped them to better adapt and regulate their behavior to fit the situation in agreement with individually chosen goals and values and may thus have protected them from developing uncontrolled drug use behaviors and opioid dependence (14). In contrast, low Self-Directedness is an element of an immature personality profile, which is often found in addicted people. Therefore, higher scores on scales for Reward Dependence and Self-Directedness may have protected the never-dependent illicit opioid users from losing control and becoming addicted. The higher Self-Transcendence levels in never-dependent illicit opioid users compared to the other two groups suggests that they were susceptible to fantasy and daydreaming, and this is enhanced by the use of opioids (11). Therefore, high Self-Transcendence in never-dependent illicit opioid users may have been involved in the choice to experiment with opioids. Furthermore, the high level of Harm Avoidance in never-dependent illicit opioid users may be related to their use of opioids in order to control anxiety and to overcome feelings of inadequacy as is indicated by the fact that the highest Harm Avoidance scores were found in the dependent opioid users, somewhat lower Harm Avoidance scores in the never-dependent illicit opioid users, and the lowest Harm Avoidance scores in the healthy controls. In contrast to our hypothesis, never-dependent illicit opioid users had similar Novelty Seeking scores compared to dependent opioid users, but consistent with our expectations, never-dependent opioid users had significantly higher Novelty Seeking scores than healthy controls. These findings suggest that Novelty Seeking is a risk factor to start using illicit opioids but not a specific risk factor to develop opioid dependence.

Unexpectedly, Novelty Seeking was not very high in the dependent opioid users, although this has been found in several previous studies (11–16). However, the
dependent opioid users were addicted for a much longer period and were older than those in most of the previous studies (11,13–15). This may explain the difference between the present finding and earlier studies.

Lower Self-Directedness and Cooperativeness and higher Self-Transcendence compared to healthy controls was found in both dependent opioid users and never-dependent opioid users, indicating the presence of an immature or frail personality (13) in illicit opioid users. Consistent with earlier studies, we found that dependent opioid users scored significantly higher on Harm Avoidance and Self-Transcendence and significant lower on Reward Dependence, Self-Directedness and Cooperativeness than healthy controls (11,13–16). From these results we can conclude that the opioid dependent and healthy control samples are congruent with samples in previous studies and that differences between never-dependent illicit opioid users and dependent opioid users and healthy controls cannot be attributed to sample specificity.

Besides several study strengths, such as the relatively large study groups and the inclusion of never-dependent life-time illicit opioid users, some study limitations need to be considered. First, this is a retrospective study, and it is, therefore, not possible to determine whether differences in personality traits are a cause or a consequence of drug use and dependence. A second limitation is that there is still a chance that some of the never-dependent opioid users did become dependent after participation in the study. To minimize this risk, first opioid use had to occur at least 2 years before the start of the study - in order to include subjects that had not become dependent in the first 2 years after using illicit opioids - and a maximum lifetime opioid use of 100 times was set. Thirdly, not all character dimensions remain stable during life. Personality traits are susceptible to change over time (24), in particular Novelty Seeking, Self-Directedness and Cooperativeness (25). The groups differed in age, but all group comparisons were adjusted for age. Finally, gender influences the risk of drug use, with men being more likely to use drugs than women (26). Moreover, some studies have found that opioid drug use in women tends to escalate more rapidly than in men (27). In the present study, the group of never-dependent opioid users contained more females than the groups of dependent opioid users. However, all group comparisons were adjusted for gender.

The current findings are important for the planning of prevention strategies, because TCI personality profiles can be used in the screening of youngsters in order identify those adolescents with an increased risk for illicit opioid use and dependence, and for a personalized intervention based on their personality profile (28,29).

In summary, never-dependent illicit heroin users may have started to use heroin partly due to their tendency to seek novel and/or spiritual experiences (high Novelty Seeking, high Self-Transcendence) and their tendency to avoid aversive stimuli (high Harm Avoidance), whereas they may have been protected against the development of
dependence by their need for social approval (high Reward Dependence) and their self-efficacy (high Self Directedness).

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**Contributors**

Authors Jan M. van Ree, Wim van den Brink, Vincent Hendriks and Mary Jeanne Kreek designed the study and wrote the protocol. Authors Eline R. Zaaijer, Jessica Bruijel and Wim van den Brink managed the literature searches and summaries of previous related work. Authors Eline R. Zaaijer, Jessica Bruijel, Peter Blanken and Maarten W.J. Koeter undertook the statistical analysis, and author Eline R. Zaaijer wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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18. van den Brink W, Hendriks VM, Blanken P, Koeter MWJ, Zwieten BJ, van Ree JM. Medical prescription of heroin to treatment resistant heroin addicts: two


Supplementary material

Table S1. Internal consistency of TCI-105 scales in never-dependent opioid users (NDO), dependent opioid users (DO) and healthy controls (HC) (Cronbach’s alpha [95% CI]).

<table>
<thead>
<tr>
<th></th>
<th>NDO</th>
<th>DO</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novelty Seeking</td>
<td>0.68 [0.60, 0.75]</td>
<td>0.57 [0.51, 0.63]</td>
<td>0.64 [0.55, 0.73]</td>
</tr>
<tr>
<td>Harm Avoidance</td>
<td>0.82 [0.77, 0.86]</td>
<td>0.80 [0.77, 0.83]</td>
<td>0.83 [0.78, 0.87]</td>
</tr>
<tr>
<td>Reward Dependence</td>
<td>0.65 [0.57, 0.73]</td>
<td>0.60 [0.54, 0.66]</td>
<td>0.60 [0.49, 0.69]</td>
</tr>
<tr>
<td>Persistence</td>
<td>0.74 [0.68, 0.80]</td>
<td>0.65 [0.60, 0.70]</td>
<td>0.61 [0.50, 0.70]</td>
</tr>
<tr>
<td>Self-Directedness</td>
<td>0.80 [0.76, 0.85]</td>
<td>0.79 [0.76, 0.82]</td>
<td>0.75 [0.69, 0.81]</td>
</tr>
<tr>
<td>Cooperativeness</td>
<td>0.74 [0.68, 0.80]</td>
<td>0.73 [0.68, 0.76]</td>
<td>0.53 [0.41, 0.64]</td>
</tr>
<tr>
<td>Self-Transcendence</td>
<td>0.89 [0.87, 0.92]</td>
<td>0.87 [0.85, 0.89]</td>
<td>0.85 [0.81, 0.88]</td>
</tr>
</tbody>
</table>