Effect on Naltrexone on Cue-induced Craving for Amphetamine in Amphetamine Depended Individuals
Effect of Naltrexone on Cue-induced Craving for Amphetamine in Amphetamine Dependent Individuals

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Amphetamine addiction is an increasing problem affecting many people both globally and in Sweden. Approximately 35 million people worldwide abuse amphetamines, which is more than the total number of cocaine and heroin abusers combined. Among heavy drug users in Sweden, 75 percent are using amphetamine substances. At present there is no approved pharmacotherapy for amphetamine dependence.

There is growing evidence from pre-clinical and clinical studies pointing towards the involvement of the endogenous opioid system in the pathophysiology of stimulant addiction. The opioid antagonist naltrexone has been shown to modulate some of the behavioural and neurochemical effects of amphetamines in animal models. Recent clinical studies have also demonstrated that naltrexone pharmacotherapy significantly attenuated the subjective effects of amphetamine in acute and chronic dosing models in humans.

Craving is an important notion in addiction research, and is manifested both subjectively (strong thoughts and urges to take the drug) and physiologically (increased heart rate, sweaty palms etc.). In accordance with the cue-reactivity paradigm, craving can be elicited in addicted individuals when they are exposed to different types of cues associated with drug taking. Such laboratory paradigms also serve as useful methods to evaluate potential pharmacotherapies that target specific and complex features such as craving.

The aim of the present human laboratory study was to investigate the effect of an acute dose of naltrexone on cue-induced craving for amphetamine in dependent persons. The primary hypothesis was that pre-treatment with naltrexone would attenuate the cue-induced craving for amphetamine. The study was a double-blind placebo controlled within group design and the test sessions took place at Magnus Huss clinic, Karolinska Institutet and Kronoberghäkert. A total of six amphetamine dependent males underwent the testing. Subjective craving was measured using a single item visual analog scale, and the physiological craving was measured as difference in blood pressure and heart rate.
METHOD

Research subjects
Six male amphetamine dependent volunteers* (see comments and conclusion) between the ages of 24 and 44 years (SD = 6.7, mean age = 34 years) were recruited for the study. One of them came from KI and surrounding environment, and the other five were recruited in Kronobergshäktet, a prison located in central Stockholm. The subjects were screened and recruited by a coordinator at Kronobergshäktet who meets all new inmates. The inclusion criteria for subjects to participate in the study were (1) man between the ages of 20 and 55, (2) fulfils DSM-IV criteria for amphetamine dependence, (3) drug free from amphetamine between 2 and 30 days, (4) history of intravenously amphetamine abuse and (5) at least two years of amphetamine abuse. Subjects were excluded if they (1) fulfilled DSM-IV criteria for any dependence other that amphetamine, (2) fulfilled DSM-IV criteria for any major psychiatric diagnosis, (3) suffered from any major somatic diagnosis, (4) regularly used opioid analgesics, (5) had used naltrexone in the past three months or were allergic to naltrexone.

All the subjects included in the study signed a consent form, which clearly outlined the study procedure and possible side-effects of the drug. All participants received an equivalent of 50 € for their participation in the study. The study was approved by KI ethics committee and the Swedish Medical Products Agency and conducted in accordance with good clinical practise (ICH GCP, 1996) and the Declaration of Helsinki.

Procedure
The study was a double-blind placebo controlled within group design. The test sessions took place at Magnus Huss clinic, Karolinska Institute and Kronobergshäktet. The subjects were randomized to receive either 50 mg naltrexone or an identical placebo at two separate test sessions with 7 days interval. After intake of the naltrexone/placebo, the subject waited approximately one hour post which he was exposed to two different types of cues (active and neutral) with 30 minutes interval. The active cue was a 5 minute video displaying drug paraphernalia and people in different drug taking rituals, designed to illicit craving in accordance with the cue-reactivity paradigm. The neutral cue was a video displaying a 5 minute excerpt from a “National Geographic” episode. The order of the cue-presentation was randomised between subjects, but each subject was exposed to the cues in the same order on both test days. After each cue-exposure, as well as at the start of each session (baseline measurements), the subject underwent a battery of tests comprised of both subjective and physiological measures. The specific cues and measurements were tested in an earlier pilot study, designed to evaluate the effectiveness of the cues in inducing craving in amphetamine dependent individuals compared to age and gender matched healthy controls (Nitya Jayaram-Lindström, unpublished data, 2005).

On the test day the subjects were asked to abstain from nicotine and caffeine. To be included in the study, all patients had to be drug free for a minimum of two days prior to testing as well as the seven days between the test sessions. Because of practicalities at Kronobergshäktet urine testing were not conducted but given the high security at the prison facility and the subjects own affirmations, it is likely but not certain that the subjects abstained totally from illicit drugs during the week of the study. At Magnus Huss, the testing was done in the laboratory room, while at Kronobergshäktet it was conducted in visitor and interrogation rooms.
**Subjective measurements**

The subjective levels of amphetamine craving were measured using a single item visual analogue scale asking the subject to estimate his craving for amphetamine on a scale from 0 to 100. See table 1 for the description of the scale the subjects received each time they answered the question. To assess the general mood-state of the subjects, the Profile of Mood scale (POMS) was used. All subjective measures were conducted at baseline (before intake of naltrexone/placebo) and after both the active and neutral cues.

**Table 1.** Single item amphetamine craving question evaluating the subjective craving in the subject.

<table>
<thead>
<tr>
<th>Estimate your current craving for amphetamine on a scale from 0 to 100</th>
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<tr>
<td>0 = I feel no craving for amphetamine at all.</td>
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<tr>
<td>50 = I feel a distinct psychological (strong thoughts, urges etc.) and physiological (increased sweat production etc.) craving for amphetamine.</td>
</tr>
<tr>
<td>100 = I feel the strongest craving possible for amphetamine and nothing else occupies my mind and body. If I had access to amphetamine right now it would be impossible to resist intake.</td>
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**Physiological measurements**

Blood pressure and heart rate were recorded automatically. All physiological measures were conducted at baseline (before intake of naltrexone/placebo) and after both the active and neutral cues.

**Data analysis**

The primary hypothesis of the study was that pre-treatment with naltrexone would attenuate the cue-induced craving for amphetamine. The primary outcome measure was the difference in the craving score between the two treatment conditions (ie naltrexone and placebo) and between the two cue sessions (ie active and neutral cue).

The secondary outcome measure was to assess whether pre-treatment with naltrexone also attenuates the physiological craving as measured by change in blood pressure and heart rate.
COMMENTS AND CONCLUSIONS

The study was to include 20 amphetamine dependent individuals but due to certain restrictions at the Kronobergshäktet, the local prison in central Stockholm and in addition the issue of expiration of the medication the study could not be completed as planned. There are however ongoing plans to add more patients and complete the project. Thus results are pending.
REFERENCES


