Naltrexone Implant for the Treatment of Polydrug Dependence:
A Randomized Controlled Trial

BACKGROUND:

- Only effective treatment for opioid dependence is the substitution of one opioid for another
- Oral naltrexone has been shown to decrease amphetamine use compared to placebo but is ineffective in the treatment of opioid dependence due to poor treatment adherence
- The naltrexone implant could bypass the problem of treatment adherence and be used to treat patients with heroin-amphetamine polydrug dependence

OBJECTIVE:

- To study the overall real-world effectiveness of the naltrexone implant in the treatment of heroin-amphetamine polydrug dependence

METHODS:

- **Design**
  - Double-blind, randomized, parallel, controlled experimental; Duration: 10 weeks
- **Inclusion/exclusion criteria**
  - Inclusion: Primary DSM-IV diagnosis of concurrent amphetamine and opioid dependence for at least 1 year, between 18 and 50 years old, high school graduate or above, negative urine toxicology and alcohol breath test, no current use of psychotropic medications, at least one relative willing to participate in the treatment, a stable address, a home telephone number, willingness and ability to give informed consent and participate, and a negative pregnancy test and use of adequate contraception for women of child-bearing age
  - Exclusion: Clinically significant cognitive impairment, schizophrenia, a paranoid disorder, bipolar disorder, seizure disorder, advanced neurological, cardiovascular, or hepatic disease, active tuberculosis, a current febrile illness, an AIDS defining illness, significant lab abnormality such as severe anemia, unstable diabetes, or liver function test results greater than 3 times normal values, pregnant, pending legal charges with potential for impending incarceration, concurrent participation in another treatment study, and concurrent treatment in another substance abuse program
- **Outcome measures**
  - Primary outcome measures: Retention in the study, proportion of urine samples that were free of both amphetamine and opioids during the treatment, and improvement on the CGI
  - Secondary outcome measures: Proportion of opioid free urine samples during treatment, proportion of amphetamine free urine samples during treatment, GAF score, number of days per week that amphetamine was used during treatment, craving for opioids and amphetamine, and adverse events
- Number of patients enrolled
  - 50 patients assigned to each treatment group
- Drug regimens/dosages used
  - 1000 mg of naltrexone as a subcutaneous implant or a placebo implant identical in appearance
- Power
  - Power was not reported in the study
- Data handling method used
  - Intent-to-treat

RESULTS:

- 14 patients in the placebo group and 26 patients in the naltrexone group completed the study
- **Primary Outcomes**
    - Retention rate: 52% for the naltrexone group and 28% for the placebo group ($p = 0.01$)
    - Proportion of drug free urine samples: 38% in the naltrexone group and 16% in the placebo group ($p = 0.01$)
    - 56% of naltrexone patients showed much or very much improvement according to CGI compared to 14% of placebo patients ($p < 0.001$)
- **Secondary Outcomes**
    - Heroin free urine samples: 52% of the naltrexone patients and 20% of placebo patients ($p < 0.001$)
    - Amphetamine free urine samples: 40% of the naltrexone patients and 24% of placebo patients ($p = 0.09$)
    - The mean number of amphetamine use incidents in times/week was 4.5 times for the naltrexone group and 5.7 times for the placebo group ($p = 0.06$)
    - 83.3% of patients in the placebo group and 13.6% of patients in the naltrexone group Reported full effect from amphetamine use ($p < 0.001$)
    - Mean GAF scores: 82.0 for the naltrexone group and 71.9 for the placebo group ($p = 0.004$)
- Authors' Conclusion
    - Relative to placebo, the naltrexone implant resulted in higher retention in the study, decreased heroin and amphetamine use, and improved clinical condition of patients, which provided evidence of the first effective pharmacologic treatment for heroin-amphetamine polydrug dependence

STRENGTHS:

- Randomized placebo-controlled trial, double-blind

LIMITATIONS:

- Possibility of false positives on urinalysis, subjective nature of the reporting of CGI and GAF scores, possible inadequate power and alpha, small sample size, short duration of study, missing occasional heroin use on weekly urine tests due to only being able to detect use for up to 3-4 days, administering an insufficient dose of the naltrexone implant, and inappropriate inclusion criteria such as including only those with a high school degree and above, as well as those with a stable address and home telephone number

CONCLUSION:

Further research is needed to determine the effectiveness of the naltrexone implant in polydrug dependent patients. The study should be powered to at least 80% with an alpha of 0.05. To eliminate the chance of detecting a false-positive on urinalysis, confirmatory tests should be used. Also, if heroin is the opioid of interest, 6-acetylmorphine should be the metabolite that is screened for because it is specific to heroin. An additional outcome measure to consider would be to evaluate the perceived "high" experienced after using heroin. A patient may yield a positive result for heroin use, but the actions of the heroin could have been antagonized by the naltrexone. Patients should also have an appropriate number of urine analyses to detect all substance use. An appropriate dose of the naltrexone implant should be administered and the duration of the study should be sufficient to apply the results to clinical practice.

Reference: Tiihonen, J. et al. Naltrexone implant for the treatment of polydrug dependence: a randomized controlled trial. Am J Psychiatry. 2012; 10.1176/appi.ajp.2011.11071121

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