CASE REPORT

Naltrexone may block euphoria-like placebo effect

Andriy V Samokhvalov,^{1,2,3} Islam Gamaledin,^{1,4} Beth Sproule,^{3,5,6} Jürgen Rehm^{2,3,7,8–10}¹Addictions Program, Centre for Addiction and Mental Health, Toronto, Canada²Social & Epidemiological Research Department, Centre for Addiction and Mental Health, Toronto, Canada³Department of Psychiatry, University of Toronto, Toronto, Canada⁴Institute of Environmental Studies and Research, Ain Shams University, Cairo, Egypt
⁵Pharmacy Program, Centre for Addiction and Mental Health, Toronto, Canada⁶Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada⁷Dalla Lana School of Public Health, University of Toronto, Toronto, Canada⁸Institute of Medical Sciences, University of Toronto (UofT), Toronto, Canada⁹PAHO/WHO Collaborating Centre for Mental Health & Addiction¹⁰Epidemiological Research Unit, Technische Universität Dresden, Klinische Psychologie & Psychotherapie, Dresden, Germany**Correspondence to**

Dr Andriy V Samokhvalov, avsamokhvalov@yahoo.ca

SUMMARY

Naltrexone is a first-line treatment for alcohol use disorders in North America and Europe. It was prescribed to a 63-year-old patient in order to help control amounts of alcohol consumed per drinking occasion. The patient experienced a paradoxical, but consistent side effect of feeling inebriated each time he took naltrexone. In order to investigate this phenomenon we administered naltrexone and a placebo in a randomised double-blind fashion. The patient exhibited a 'high-like' response to all placebo capsules and a decrease in the subjectively perceived euphoria shortly after ingestion of naltrexone. Given that this placebo effect could be mediated via opioid receptors we suggest that this case illustrates the ability of naltrexone to eliminate the placebo effect. This feature of naltrexone, upon further investigation, might be used in randomised clinical trials in addition to or as an alternative to a placebo.

BACKGROUND

Naltrexone is a first-line treatment for alcohol use disorders in North America and Europe.¹ This medication has demonstrated effectiveness both in clinical trials and in clinical practice. Naltrexone blocks opioid receptors that are involved in major reward pathways, thus reducing the positive reinforcement effects of opioids and alcohol. Moreover, it has been reported that naltrexone has potential in the treatment of eating disorders and pathological gambling. Naltrexone has contraindications and side effects, but our patient experienced a feeling of euphoria that has not been listed as a side effect. This finding contradicted expectations based on the mechanism of action of naltrexone and thus drew our attention and called for further investigation. Our double-blind naltrexone/placebo trial demonstrated two important points:

1. Euphoria experienced upon the administration of naltrexone is likely a placebo effect that lasts until naltrexone takes effect
2. Naltrexone may have a placebo effect blocking properties, which have not been described before, and after further research might be used in clinical trials when placebo use is limited due to certain reasons.

CASE PRESENTATION

The patient is a 63 year-old man employed as an engineer. He came to our clinic because of problematic drinking. He had his first drink at the age of 11 years, started drinking regularly (4–5 SD/week) at the age of 18 years and since the age of 20 years was drinking problematically (mostly

binging). At initial assessment the patient drank most days of the week (5–7 days), usually consumed up to 4 standard drinks per occasion, beer or wine, in the evening, with an absolute maximum of 7 standard drinks per occasion in the last month. The patient identified stress and marital discord as his major triggers. He also stated that his alcohol consumption has affected his relationships and he admitted to having a history of driving under the influence in the past. He tried to stop or cut down his drinking on his own with the longest period of abstinence being 3–4 days. The patient reported that he was a former smoker and was not using any other substances (confirmed by routine urine drug test). Medical history: hypercholesterolaemia and history of myocardial infarction, coronary artery disease and recent bypass surgery. Medications: prescribed atorvastatin, ezetimibe and acetylsalicylic acid. No history of mental disorders. Family history: one of the patient's daughters was diagnosed with bipolar affective disorder. No significant abnormalities were found during physical and mental examination. Blood alcohol content was zero. The patient met DSM-IV criteria for alcohol abuse and was prescribed naltrexone in an initial dose of 25 mg/day.

The patient returned to the clinic 5 days later stating that he had had an unusual reaction to naltrexone: immediately, 'within 30–60 s', after taking it he felt 'high', namely he felt euphoric, described symptoms of derealisation, and had impaired motor coordination. It must be noted that the patient had not been drinking for at least several days before taking naltrexone. These initial symptoms were followed by irritability, poor impulse control and intense headache. On the morning of the day of the visit, the patient took a lower dose of naltrexone, 12.5 mg, and experienced similar symptoms. These symptoms had mostly subsided by the time of seeing his physician (1 h after taking the medication) and there was neither objective evidence of having these side effects nor their comprehensive description. We could not find any previously documented cases reporting similar side effects, specifically euphoria as the patient described his state as 'feeling high' and 'like having had 2–3 drinks'.

INVESTIGATIONS

In order to document the patient's responses to medication and investigate potential placebo effects the patient agreed to observed administration of test doses of placebo and naltrexone (12.5 mg). The naltrexone one-fourth tablets were over-encapsulated, and matching lactose filled placebo

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capsules were prepared by the CAMH pharmacy. To maintain double-blinding, the capsules were dispensed in a blister pack specifying which three capsules to be given to the patient in 1 h intervals on two separate days that were 1 week apart. The test dose schedules were placebo–naltrexone–placebo and placebo–placebo–naltrexone, with each schedule assigned in random order to one of the two study days. The patient's vital signs were monitored by the study nurse and the subjective high assessment scale (SHAS)² was used to monitor the patient's subjective responses before and after each capsule administration and at the end of each study day. The patient completed the SHAS when deemed appropriate and the study nurse performed additional vital signs checks, if the patient felt significant change in his physical or mental status. There were no significant abnormalities in his vital signs during the period of testing.

On day 1 (placebo–naltrexone–placebo), the patient scored 1 on the SHAS, just before the administration of the first placebo pill. He began to feel euphoric and the SHAS score significantly increased within next 40 min (see figure 1) and decreased again 20 min after administration of 12.5 mg of naltrexone. Then, the patient started to feel progressively more euphoric and the SHAS scores increased gradually back to higher values and stayed high after administration of the second placebo pill.

On day 2 (placebo–placebo–naltrexone) the patient scored 1 on the SHAS, that increased to 14 within 20 min after administration of the first placebo pill and with some fluctuation went further up to 16 by the time of administration of the second placebo pill. All this time the patient felt 'high' and described his condition as 'like being drunk'. After that the SHAS scores gradually declined until naltrexone was ingested. After administration of naltrexone SHAS scores dropped further and the patient returned to normothymic state.

DIFFERENTIAL DIAGNOSIS

The patient met the DSM-IV criteria for alcohol abuse and no differential diagnosis was necessary.

TREATMENT

After unexpected initial response to naltrexone, other therapeutic options were discussed with the patient. He was

prescribed topiramate which was gradually titrated to 100 mg/day (50 mg twice a day). While taking topiramate the patient had virtually no cravings for alcohol, nor experienced any positive reinforcement when drinking—he consumed alcohol on two occasions in the course of the subsequent 3 months, consuming one glass of wine on each occasion.

OUTCOME AND FOLLOW-UP

The patient successfully stopped drinking on topiramate (50 mg orally, twice daily). He also attended the 21-day residential programme at CAMH, during which he improved his understanding of his triggers and underlying psychological mechanisms of his drinking and developed skills to cope with them.

DISCUSSION

We were not able to locate any cases of euphoric reactions to naltrexone. Originally we attributed this reaction to changes in balance between μ -opioid receptors and κ -opioid receptors, that is, while blockade of μ -opioid receptors normally diminishes positive reinforcement from alcohol, blockade of κ -receptors, which are responsible for dysphoria, potentially might elicit euphoria-like response. Though this hypothesis could be supported by recent studies indicating that κ -opioid receptor antagonists have potential in the treatment of depression and anxiety,³ our trial showed that the patient responded exclusively to the placebo. Specifically, the patient experienced euphoria and his 'high' scores increased each time following four placebo administrations and decreased after the two naltrexone administrations. This pattern makes it very unlikely to be attributable to chance alone—the probability of such an event is 1.56% given equal chances of either outcome (response vs no response). A review of the details of the patient's responses to naltrexone/placebo during the trial and his original response to naltrexone yielded the following:

1. The patient's original response to naltrexone was immediate, that is, within 30–60 s of administration, which may not be attributable to the medication itself due to a delay in the onset of effect during the absorption phase, and thus should be treated as a response to the event of taking medication or placebo effect.

Figure 1 Dynamics of the patient's responses to administration of placebo/naltrexone.

2. The patient's responses were not consistent, that is, different SHAS items were chosen each time and the timing of responses varied to a great extent.
3. The timing of the return of increased SHAS scores following naltrexone administration on the first study day is not consistent with the proposed mechanism.

Interestingly enough, when detailed medical history was reviewed the patient admitted that several years ago he was prescribed oxycodone for pain management and it felt exactly the same way he felt when he ingested naltrexone for the first time. In our opinion, it explains the euphoria-like nature of placebo effect in this patient: he was aware that naltrexone is an opioid receptor antagonist and the use of opioids such as oxycodone is a contraindication for the use of naltrexone. Consequently, oxycodone, opioids and naltrexone were mentioned several times before naltrexone was prescribed and since the only association that patient had with these words was previously experienced euphoria we might assume that he had subconsciously evoked the response that was similar to the one he experienced several years ago.

Overall, the patterns of responses to placebo and naltrexone preparations indicate that euphoria described by the patient is a placebo effect and there are some indications why this effect was such.

Another most important finding was based on the fact that the patient's euphoria subsided quickly after taking naltrexone (second capsule on day 1 and third capsule on day 2), which was not observed when the patient's next administration was placebo (second capsule on day 2) or when it was the final administration (third capsule on day 1)—the euphoria lasted for 2 h. Given that placebo effects can be, and in the case of euphoria-like placebo effects are, mediated via μ -opioid receptors,^{4–6} their blockade by naltrexone may result in the negation of placebo effects. This hypothesis is supported by the observations of Eippert *et al*⁷ who showed that another opioid receptor antagonist, naloxone, reduces placebo-induced responses in cortical structures responsible for pain modulation in their case.

We believe that this placebo-effect blocking the property of naltrexone should be further investigated (eg, on a group of subjects large enough for proper statistical analysis) and has potential application in complex clinical trial designs as an adjuvant to placebo or in cases when placebo use is not possible or is ethically inappropriate.

Learning points

- ▶ Euphoria-like effects experienced when taking naltrexone are likely to be attributable to the placebo effect and tend to subside when naltrexone takes effect.
- ▶ Naltrexone might have placebo-effect blocking properties which potentially can be used in complex clinical trial designs (eg, as an adjuvant to placebo).
- ▶ Euphoria-like presentation of placebo effect is likely to be related to previously experienced effects of prescription opioids.

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Contributors AVS was the main healthcare provider of the patient, designed and conducted the trial and prepared the manuscript. IG also provided medical services to the client, participated in research pertinent to the study subject, and took part in interpretation of results and manuscript preparation. BS participated in trial design and was responsible for preparation of medications and manuscript preparation. JR was responsible for trial design, interpretation of results and manuscript preparation.

Competing interests None.

Patient consent Obtained.

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