OPEN PEER REVIEW

Open Peer Review (OPR)

As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
- Authors' satisfactions from the review process: Increases honesty between authors and reviewers
- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:
https://brieflands.com/briefland/knowledgebase/category/tree.html#opr.html

Archives of Neuroscience
Article DOI: 10.5812/ans.121361
Published in: Archives of Neuroscience: 9(1); e121361

Peer Review Report for "Testosterone Improved Hyperalgesia in a Patient Under Methadone Maintenance Treatment"

Author(s): Nader Charkhgard, Shahram Naderi, Kamyar Ghani, Mahboubeh Manouchehrabadi

Review Timeline:

Submit Date: 22 Nov 2021
Revised Date: 18 Jan 2022
Accepted Date: 24 Jan 2022

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Ali Yoonessi: Reviewer | Revision (0)

28 Dec 2021

Dear AE,
The manuscript entitled “The role of testosterone on hyperalgesia in patients using methadone” describes a case in which presented with hyperalgesia due to opioid use and after testosterone administration, improved clinically. This is a very interesting case, and I would like to share it with my colleagues if or when it is published. Before my recommendation for publishing this article, I would like to ask authors to make a few changes:
• If the journal instruction allows, the abstract could benefit if you remove the structured format, which is most suitable for research articles, and not case report (e.g. remove the subtitle “methods”)
• There are some general knowledge in the first few paragraphs that can be removed (for example, most of the first paragraph). Instead please have a more in-depth review of the OIH and OPIAD.
• Grammatical errors such as the sentence ending with “…,hyperalgesia caused by narcotics” (line 29) or line 46. There are more. Please revise the whole text to make sure

the grammatical errors are corrected.

• There are some discussions in the middle of the case description. Please put a title for the section “case description” (instead of case report), move the discussion paragraphs to the proper section (e.g paragraphs starting at line 52 and 63)

• The tables can be converted to graphs, which would be much more descriptive. Table 1 can be converted to a timeline, where events are marked, and table 2 and 3 can be converted to a bar or line graph.

• In the discussion and conclusion part, possible other related cases, possible mechanisms, and possible other relationships should be briefly, but in-depth reviewed.

Thanks.

REFEREE: Associate Editor | **Revision** (0) 1 Jan 2022

Dear EIC

The reviewer(s) have recommended publication, but also suggest some minor revisions to the manuscript. Therefore, I invite the author to respond to the reviewer(s)' comments and revise his manuscript.

Kind regards,

REFEREE: EIC | **Revision** (0) 1 Jan 2022

Dear Author,

Your article is reviewed by the reviewers carefully. According to their comments, this document needs minor revision. Please follow their comments as requested.

Thanks.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Dear Reviewer

Greetings and Regards

Thank you very much for your comments.

The changes you wanted were made:

- Due to the case report structure, the method of conducting the study was mentioned in the Introduction section.
- According to your order, some information was removed from the beginning of the study and explanations about hyperalgesia in patients were mentioned.
- Grammar corrections were made
- Changes were made to the Case Description
- The tables was changed to graph and figures
- In the discussion and conclusion part, changes were made to further describe the possible mechanisms and their relationship to the reported case.

Thank you very much for your attention

Case report

Testosterone Improves Hyperalgesia in a Patient under Methadone Maintenance Treatment

Abstract

Background: Long-term use of narcotics causes hyperalgesia in some patients with an unknown mechanism known as opioid-induced hyperalgesia (OIH). Methods: a forty-three old man suffered from the effects of Opioid-induced hyperalgesia syndrome due to long-term use of methadone. Testosterone was prescribed. Result: Testosterone prescription significantly reduced the hyperalgesia. Conclusions: Testosterone may have a therapeutic value in opioid-induced hyperalgesia.

Keywords: opioid; hyperalgesia; testosterone

Introduction

Opioids refer to a category of natural and synthetic products, which are mostly used for ache management and opioid dependency [1]. Opioids are mighty analgesics and are widely prescribed for the management of acute and chronic pain and their use has quickly grown in current years[2, 3].They exert their analgesic outcomes by means of binding to opioid receptors in the brain and spinal twine, which in turn coupled with G-proteins. This leads to the block of calcium and potassium channels, which in turn decreases the neuronal excitability [4, 5]. Opiates potently suppress the hypothalamic-pituitary-gonadal axis [2, 3].

Testosterone plays a vital role in the development of male reproductive organs and other sexual traits such as the growth of body hair, bone and muscle mass [6, 7], and body composition [8, 9]. It also changes behavior and life style. Decreased levels of testosterone can result in reduced libido, fatigue,

reduced muscles mass, osteopenia[9, 10], diabetes, osteoporosis, and bone loss[6, 7]. This syndrome is often called opioid induced androgen deficiency (OPIAD)[9, 10]; Testosterone treatment in men with hypogonadism has a therapeutic effect on many male disorder[10]. Another symptom of patients with substance use disorders is hyperalgesia due to the drug abuse and the factors affecting it [11]. Male hypogonadism refers to a condition in which the body is unable to produce enough testosterone [12, 13]; various conditions and diseases can reduce testosterone levels in men, for example taking certain medications and drugs (14).

Is pain a unique sensory experience that reflects each person's perception of the threat to their health? One of the factors influencing the tendency to use drugs, especially narcotics, is pain [13, 14], and in particular chronic pain; On the other hand, chronic pain is also very common in people receiving opioid agonists. This chronic pain during maintenance therapy with agonists is one of the reasons for increasing the dose of agonists (methadone), which paradoxically causes progressive pain in patients [15].

Opioid-induced hyperalgesia (OIH) may be a development whereby opioids increase patients' pain sensitivity, complicating their use in physiological condition.[11, 14]. OIH is a paradoxical reaction in which the patient takes drugs to treat pain, but actually becomes more sensitive to painful stimuli [15]. Very little is known about the prevalence of OIH [15]. However, the prevalence of OIH seems to be high among opioid patients [16]. Cold Pressor test (CPT) is a well-known test to help identify hyperalgesic patients [16]. In this study, CPT was used to diagnose and follow-up hyperalgesia in patients. To do the CPT, a plastic cooler was filled with ice packs and filled it nearly two-thirds complete of water. Add crushed ice to the water to keep the water temperature around 2 ° C so that the water temperature does not change much as we record the pain. During the test, the patient sits down. Dip one hand into water (up to 1 cm above the wrist), keep the hand open and not to touch any of the ice packs. The amount of time that patient can tolerate is a determinant of his sensitivity to pain. This test is used to determine the pain sensitivity threshold (pain onset time) and pain tolerance (maximum time the person tolerates) [18, 17].

Possible mechanisms concerned in OIH include involvement of central sensitization with glutaminergic activation and genetic mechanisms. The two most widely used methods for treating these patients are NMDA antagonists and opioid rotation. However diagnostic criteria have not yet been well defined [15].

Case Description

The patient was a male with moderate education (Diploma), age (43 year), average height (171cm) and weight (85 kg). His personal hygiene was good. He was maintaining good eye contact. His sitting posture was much relaxed. The patient seems quiet motivated to seek treatment.

The patient has been using drugs for 20 years (graph 1). He started smoking and cannabis use at the age of 19, and stopped using cannabis two years later. From the age of about 20, he sometimes took prescription drugs (acetaminophen codeine) due to pain in the knees. He started using opium at the age of 23. He tried to quit using drugs 6 times (detoxification without drug methods and using buprenorphine), the maximum period of non-use of the patient is 3 months. Until 5 years ago, he used opium and opium juice and then methadone maintenance treatment was started for him. In the last 3 years, he has not used opium and its derivatives and other abused drugs (according to his self-

declaration and twice a month test in the clinic). There is no substance abuse in the patient's family. In the workplace, two sick employees use drugs.

Most of the routine tests (CBC diff & LFT) of the patient were normal except for the reduction of free and total serum testosterone levels.

Once a week, 100 mg of testosterone was injected intramuscularly for the patient. This treatment was continued for 3 months. During this period, a monthly CPT was performed for the patient and no change (decrease or increase) in the amount of methadone received was given. The patient's testosterone level was measured 3 months later (Figure.1).

The patient's sexual desire is better, he has more energy to do daily tasks and he is less tired. Patient hot flashes have only occurred once in the last 3 months. The patient's abdominal circumference has been reduced to 102 cm (although he has been on a diet). The patient's testosterone level is increased to a higher degree (Figure.1). Without reducing the amount of methadone consumed by the patient during this period, from the first month onwards, the time of feeling the pain and the patient's maximum ability to hold his hand in ice water gradually increased (Figure.2).

Discussion

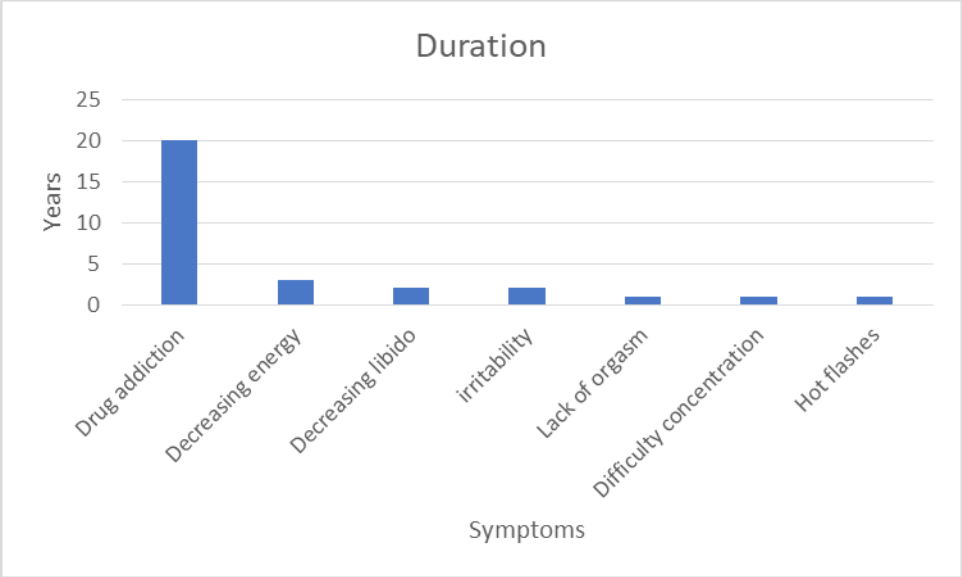
Some believe that the prevalence of OIH is related to gender and somehow it is associated with fibromyalgia. Fibromyalgia is more common in women, and since one of its new treatments is testosterone; There is evidence that low testosterone levels are associated with pain [16, 17], and taking testosterone supplements has improved the patient's condition and improved pain perception. In the mentioned patient, the symptoms were controlled and improved by taking testosterone and not reducing the dose of narcotics, hyperalgesia caused by narcotics.

At the beginning of the study, the patient's complaints included hyperalgesia, decreased libido, and failure to orgasm, decreased energy, difficulty concentrating, hot flashes, and irritability. Decreased testosterone levels may have been a factor in the patient's condition during treatment, which was largely due to hypogonadism and without any other factor (except for the patient's concentration and irritability). Especially the patient's hyperalgesia, which is performed by receiving testosterone without reducing the patient's methadone dose. Given that, apart from prescribing testosterone to treat the patient's hypogonadism, no other intervention has been performed to cure the patient's hyperalgesia, it is likely that the factor affecting the OIH process is a decrease in patients' testosterone levels.

Conclusions

Some studies have shown that the OIH is not related to the dose of the narcotics and may result from any dose of opioid; although with each dose of opioid, OIH is formed however respondents normally managed OIH by opioid dose reduction, administering a nonopioid adjuvant, or discontinuing opioids [14]. Albeit the evidence for a link between testosterone levels and OIH in patients undergoing maintenance therapy with agonists is subject to further studies, proving an association between this problem and its treatment will revolutionize it. Given that one of the reasons for the unintended increase in the dose of agonist drugs is in the treatment of hyperalgesia in patients [18], this study and case report will be very important because Proves that increasing the dose of methadone reduces the

level of testosterone in the blood and thus increases hyperalgesia in the patient; hypotheses about hyperalgesia caused by narcotics have not led to a suitable solution and treatment for these patients. In addition, it is important to remember that in many patients with OIH, there is still hyperalgesia even after stopping agonist treatment, and this may be due to the inherently low blood testosterone levels of these people, and this pain also leads to the relapse of drugs. However, drug use leads to a further decrease in testosterone in the patient and increases patients' hyperalgesia. This means that OIH occurs in patients with lower testosterone levels, and increased serum testosterone levels help treat and improve patients' OIH. Further studies are needed to link serum testosterone levels to OIH.



Graph 1- Presenting complaints and duration of the symptoms of the patient

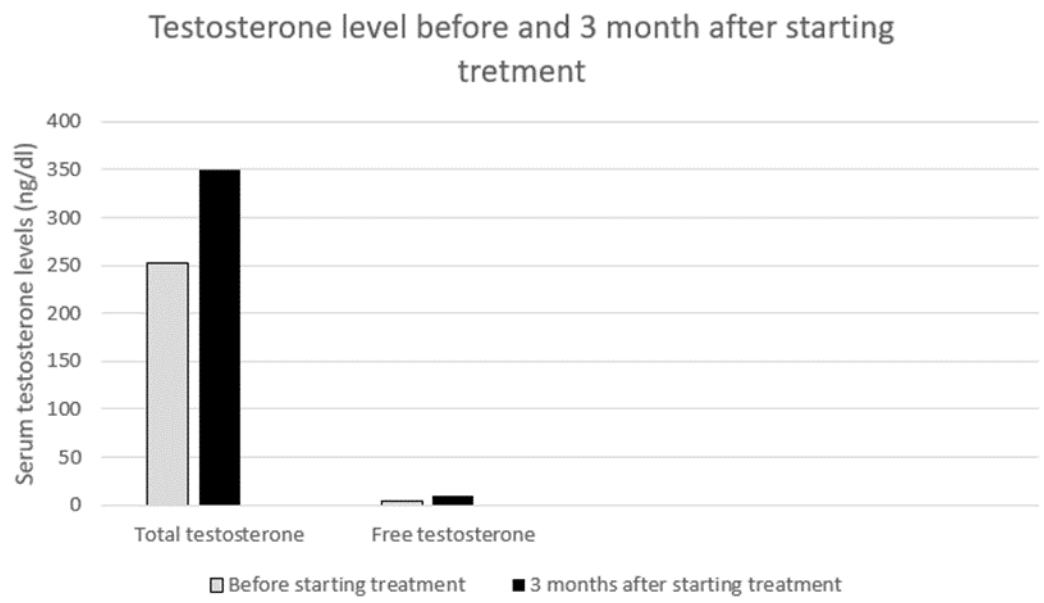


Figure.1- Testosterone levels in before and 3 months after starting treatment

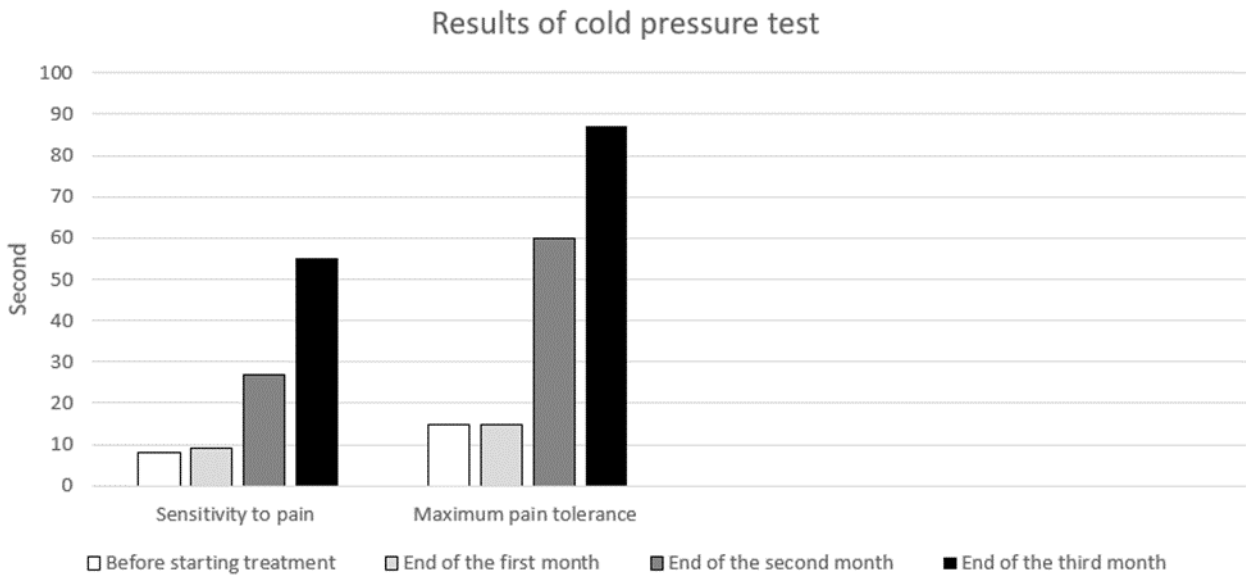


Figure.2- Results of Cold Pressure Test

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (1) — 18 Jan 2022

Dear AE,
The changes I requested were made. I recommend it for publication.
Thanks.

REFEREE: Associate Editor | **Revision** (1) — 24 Jan 2022

Dear EIC
Based on the authors' answers to the reviewers' comments, the reviewer(s) have recommended publication.
Kind regards.

REFEREE: EIC | **Revision** (1) — 24 Jan 2022

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.