CASE REPORT

Opioid-induced constipation reversal in response to placebo in a patient with a history of IBS receiving methadone maintenance therapy

Andriy V Samokhvalov,^{1,2} Jürgen Rehm¹

¹Social & Epidemiological Research Department, Centre for Addiction and Mental Health, Toronto, Canada
²Addictions Program, Centre for Addiction and Mental Health, Toronto Canada

Correspondence to
 Dr Andriy V Samokhvalov;
 avsamokhvalov@yahoo.ca

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SUMMARY

Opioid-induced constipation (OIC) is one of the major side effects in patients receiving methadone maintenance treatment (MMT). Quite often, constipation becomes a factor significantly affecting therapeutic options and choices. Currently used approaches are symptomatic and in many cases ineffective. At the same time, it is well known that the gastrointestinal system is a subject for psychosomatic influences. In this case report, we describe an unexpected outcome of placebo administration in a patient suffering from OIC since her participation in MMT. The patient participated in a triple-blind randomised placebo-controlled trial of naloxone for treatment of OIC. As part of the study crossover design, the patient received 1 week of placebo followed by 1 week of naloxone, and had significant improvement in her bowel functioning when receiving placebo, then returned to baseline during the second week of the study.

BACKGROUND

Opioid-induced constipation (OIC) is one of the most unpleasant side effects of opioid therapy and abuse.^{1–2} In methadone maintenance treatment (MMT) patients who typically receive high doses of a potent and long-acting opioid for extended periods of time, OIC becomes especially severe and has profound effects on the treatment process—it may require reducing the methadone dose to sub-optimal levels; patients might request switching to another substitution agent or to discontinue treatment. It also requires the use of laxatives, which in many cases fails to deliver satisfactory results and affect overall patient well-being and quality of life.

At the same time, gastrointestinal function is known to be heavily affected by psychological factors,³ with a few out of many examples being irritable bowel syndrome (IBS) and increased gastric secretions following emotional stress, etc. Psychotherapy has been shown to be an effective treatment for a number of gastrointestinal conditions related to over-reactivity,⁴ and, to the best of our knowledge, there has not been much work carried out in relation to constipation, especially when there has been a clear pharmacological cause identified.

We believe that our findings will illustrate the role of psychosomatic factors in development of constipation in opioid users and will stimulate the use of non-pharmacological approaches to OIC.

CASE PRESENTATION

A 47-year-old aboriginal woman was enrolled into an MMT programme 2 years earlier, and developed constipation within the first several weeks of MMT. At the time of observation, she was receiving 30 mg of methadone daily; the dose was stable for the past 5 months. The patient would have 2–3 bowel movements per week, mostly on days when she missed methadone doses or following the use of laxatives (Senna glycosides, bisacodyl, lactulose). She also smoked 20–25 cigarettes/day and consumed cannabis 2–3 times/week. No problem in alcohol or drug use was reported. The patient had a history of IBS with diarrhoea, prior to MMT, and she experienced no symptoms of this condition for the past 2 years. Also, she was diagnosed with post-traumatic stress disorder, generalised anxiety disorder, major depressive disorder and arthritis. In addition to methadone maintenance, she was taking alprazolam 0.5 mg as needed and extended-release bupropion 150 mg/day.

Given the patient's characteristics, she was deemed eligible for participation in the study, 'Oral naloxone for OIC in patients receiving methadone maintenance therapy', led by the first author (a description is available at ClinicalTrials.gov website NCT02137213).

INVESTIGATIONS

As part of the study, a number of indicators were used to monitor objective and subjective parameters of each patient, including:

1. Number of complete spontaneous bowel movements (CSBM) per week;
2. Laxative use (units) per week;
3. Bowel Functioning Index (BFI) as a comprehensive measure of bowel functioning.^{5–7}

At baseline (during the week prior to initiation), the patient had 2 CSBM and used 4 units of laxatives. Her BFI was 93.

DIFFERENTIAL DIAGNOSIS

The patient had a history of IBS with diarrhoea prior to MMT. Given that constipation symptoms developed only when she started MMT, and were dose-dependent (ie, with higher doses of methadone the patient felt more constipated), she tended to have bowel movements on days when she missed doses, so we concluded that her constipation was opioid-induced rather than being related to IBS.

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TREATMENT

Naloxone and placebo were offered as treatment options within the clinical trial protocol framework. The dose of naloxone was calculated based on the patient's methadone dose; specifically, we used the 50:1 methadone-to-naloxone ratio, so the patient's naloxone dose was 0.6 mg/day. Naloxone (or placebo) was added to the methadone prior to observed consumption at the pharmacy on a daily basis. During the study, baseline characteristics were measured—the patient had to attend the research pharmacy daily to receive her methadone and study medication doses. She was randomised into 1 week of placebo followed by 1 week of naloxone. Neither the patient, nor the dispensing pharmacists, nor the investigators, knew if the patient was receiving study medication or placebo.

OUTCOME AND FOLLOW-UP

The patient had her first CSBM in <24 h after receiving her first dose of placebo. During the placebo week of the study, the patient had seven bowel movements on 6 days. She noticed absence of abdominal discomfort as well as a painless and effortless defaecation process. Her BFI score at the end of the placebo week was 3, which corresponds to absence of constipation.^{5 7} When the patient was switched to naloxone, she started experiencing discomfort and difficulties with defaecation, with a feeling that the bowel movements were incomplete. She had three bowel movements during the naloxone week and her BFI score returned to 93. The patient was convinced that the medication was effective and requested a prescription for it to help her with her constipation symptoms (see patient's perspective). After the study, the patient continued to experience OIC symptoms and was prescribed laxatives (senna glycosides and docusate sodium), which allowed for partial improvement of bowel functioning. Several months later, the patient requested to be tapered off methadone and her constipation symptoms subsided while her methadone dose was gradually decreased.

DISCUSSION

Although the OIC is prevalent in various groups of patients (cancer and non-cancer pain, MMT patients, opioid abusers), our setting is unique, as the patient met the number of eligibility criteria to participate in the study, and specific outcomes were meticulously collected. Also, randomisation and proper blinding played a role in this case.

While we were not able to identify similar published cases, there are several randomised controlled trials demonstrating comparative effectiveness of several medications including naloxone over placebo.^{6 8} The data from our case report show marginal to no specific effectiveness of naloxone and at the same time demonstrate significant changes in bowel functioning following placebo administration. We can hypothesise that the placebo effect was achieved due to the order of medications (ie, placebo first), robust preparation process (the patient was asked to answer several questionnaires, and had comprehensive assessment and laboratory testing) and detailed description of the study procedures, which, in sum, resulted in development of a strong expectation that participation in the study would help with her constipation symptoms. Then, the fact that the patient's bowel functioning improved led her to believe that she was receiving actual medication and made her expect placebo or no response during week 2.

On the basis of the data collected and patient's feedback, we can conclude that (1) OIC can be influenced by manipulation

with psychological factors, that is, psychotherapy can be an option for treatment of OIC in certain patients, (2) psychological factors and personality features may play a role in development of OIC, (3) a patient's history of IBS, and mood and anxiety disorders, may serve as potential predictors of development of gastrointestinal disorders and justify the use of psychotherapy, (4) psychosocial aspects should be explored even in conditions that appear to be directly related to pharmacological intervention.

Patient's perspective

I started feeling constipated since the very beginning of my methadone programme and it got worse when the dose was increased. I suffered from constipation for 2 years by the time of my participation in the study. I felt bloated, full, had cramps. Defecation was painful, my faeces looked like 'rabbit pellets'. When I started taking the study medication it all went away—I felt good, I could go to the bathroom without any difficulties, I did not have any unpleasant feelings and discomfort. I thought that during that week I was taking real medication—I could feel the "funky" taste in my methadone drinks. Then when we switched to what I then thought was placebo, my constipation symptoms came back. I was very surprised to hear, several months later, that I had received placebo in the first week and medication in the second.

Learning points

- ▶ Psychosocial factors should be explored even in cases when the main aetiological factors appear to be identified (eg, Opioid-induced constipation (OIC)).
- ▶ Pharmacological factors are not the main or only factors contributing to OIC.
- ▶ Psychotherapy might be a potential treatment for some cases of OIC.
- ▶ History of IBS or other functional disorders of the gastrointestinal tract might be a predictor for development of constipation and/or responsiveness to psychotherapy.

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