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## Importance of blinding and expectations in opioid-induced constipation

*evidence from a randomized controlled trial*

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## Original Experimental

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# Importance of blinding and expectations in opioid-induced constipation: evidence from a randomized controlled trial

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### Abstract

**Objectives:** Previous studies have found little association between objective measures and the subjective experience of opioid-induced constipation. The subjective experience of opioid-induced constipation may be influenced by treatment expectations. While most trials control for treatment expectations through blinding, success rate is generally low. This study aimed to explore the association between objective measures and the subjective experience of opioid-induced constipation, while considering blinding success and treatment expectations, and other psychological factors.

**Methods:** Data from a randomized, double-blinded, placebo-controlled crossover trial including 21 healthy male participants was analyzed. Participants received either placebo, tapentadol, or oxycodone (in equipotent doses) for 14 days. They were assessed on objective and subjective measures of opioid-induced constipation (gastrointestinal transit time and the Patient Assessment of Constipation-Symptoms questionnaire, respectively), treatment guesses to indicate blinding success, and psychological factors.

**Results:** There was a strong association between objective and subjective measures of opioid-induced constipation when participants were treated with oxycodone ( $r=0.676$ ,

$p=0.006$ ). Furthermore, participants were able to guess that they received active treatment when treated with oxycodone ( $p<0.001$ ), suggesting that treatment expectations may have influenced the subjective experience of symptoms. Finally, patterns of moderate associations between opioid-induced constipation and other psychological factors emerged, although none reached significance ( $p>0.05$ ).

**Conclusions:** Results indicate that treatment expectations could play an important role in the subjective experience of opioid-induced constipation, and support the importance of assessing blinding success in study trials. Besides expectations, other psychological factors may be associated with opioid-induced constipation.

**Keywords:** gastrointestinal transit; individuality; motility; opioid-induced constipation; questionnaires.

## Introduction

Constipation is the most common side effect of opioid-treatment for chronic pain, with an estimated prevalence of 41–87% [1]. Unlike other opioid-induced side effects, opioid-induced constipation (OIC) often persists over time and may necessitate a reduction in opioid-dose, meaning less effective pain treatment [2]. Furthermore, OIC in itself can negatively impact quality of life and may cause psychological distress [2]. It could be valuable in clinical practice to be able to identify patients that are more likely to be negatively affected by OIC in order to individualize treatment plans. Yet previous clinical studies have found no association between objectively measured motility changes (e.g., gastrointestinal (GI) transit time) and symptom manifestation (e.g. measured by the Patient Assessment of Constipation-Symptoms (PAC-SYM) questionnaire) [3–8]. However, clinical studies are potentially confounded by comorbidity, co-medication and psychosocial consequences that often follow patients with OIC, and methodological issues could explain the lack of association.

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Another factor that has been shown to greatly influence patients' experiences in study trials are treatment expectations. While most trials control for treatment expectations by blinding participants (and often experimenters) to the type of treatment given, few studies actually assess blinding success [9]. For those that do, blinding success rate is generally below 50% [9]. As expectations influence treatment efficacy and side effect occurrence [10, 11], blinding success and unblinding may influence expectations towards, and the subjective experience of, OIC.

Besides treatment expectations, influenced by blinding success, other psychological factors may influence OIC. Individuals with gastrointestinal problems such as irritable bowel syndrome score higher on psychological measures such as neuroticism, pain catastrophizing, and somatosensory amplification [12–14]. These are factors related to the tendency to notice and/or worry about internal negative symptoms within the body. Such psychological factors, as well as an individual's expectations of OIC, may influence the subjective experience of constipation and modify the relationship between subjective and objective measures.

In order to be able to identify and help patients that are more likely to be negatively affected by OIC, the influence of blinding, and other psychological factors, needs to be further explored. Therefore, the current study explored 1) the association between subjective and objective measures of OIC, 2) blinding success and its potential influence on the association between subjective and objective measures of OIC, and 3) the association between OIC and the tendency to notice and/or worry about internal negative symptoms within the body. To explore these associations, a valid model of OIC was essential. Therefore, these psychological measures were included in the planning of a randomized, double-blinded, placebo-controlled crossover study in healthy volunteers, free of clinical confounders, with dose and duration of treatments maximized to induce constipation at a similar level to that experienced in clinical populations.

## Methods

### Data source

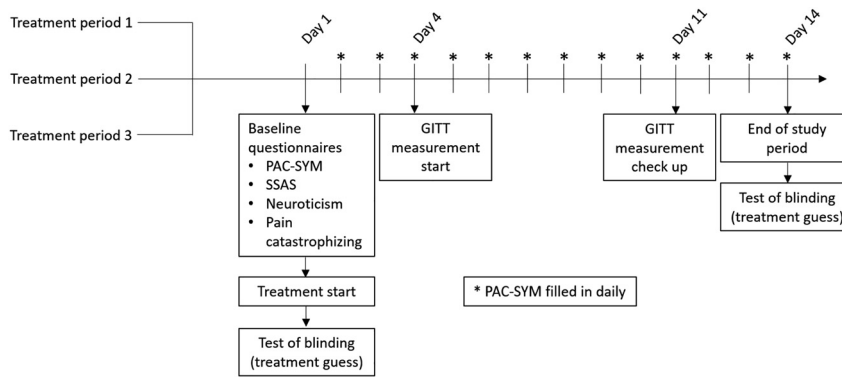
A randomized, double-blinded, placebo-controlled crossover study in healthy volunteers was designed with the main purpose of investigating levels of constipation induced by tapentadol compared to oxycodone and placebo, and has been published elsewhere [15]. In the planning of this trial, psychological measures were included for the

*a priori* purpose of investigating how these relate to subjective experience of, and objectively measured, constipation, as reported in the current study. The study was approved by the North Denmark Region Committee on Health Research Ethics and the Danish Health and Medicines Authority (reference numbers: N-20170009 and 2017041794), and was registered at [www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu) (EudraCT number: 2017-000141-52). The study took place at the Department of Gastroenterology & Hepatology, Aalborg University Hospital, Denmark. Written informed consent was obtained from all participating subjects. In the current study, OIC from the opioids tapentadol and oxycodone were investigated; tapentadol provides comparable analgesic effect to oxycodone and has been found to induce fewer GI side effects, including constipation, at equianalgesic doses [15, 16]. Each treatment condition spanned 14 days, and the washout period between conditions was at least seven days. Included subjects were male, between the age of 20–45 years, healthy, and opioid naïve (never taken opioids for a period of more than one week). The included participants ( $n=21$ ) were randomly assigned to a treatment order using a randomization list (randomization.com) generated of one block resulting in six possible sequences. Both participants and study personnel were blinded to the treatment order. Participants orally ingested equianalgesic dosages of oxycodone and tapentadol, and corresponding placebo tablets, once in the morning on day 1 and 14, and twice a day on days 2–13 (morning/evening), adding up to a total of 26 doses in each condition. Participants received verbal and written information about the potential side effects of the opioid treatment, including constipation, during the informed consent process. Figure 1 summarizes procedures relevant to the current study.

### Measures of constipation

**Gastrointestinal transit time:** GI transit time was measured using the Motilis 3D-Transit system (Motilis Medica SA, Lausanne, Switzerland) [17]. It has been described in detail elsewhere [17], but in short the 3D-Transit system uses external sensors to track the movement of an ingested electromagnetic capsule. Total GI transit time was defined as transit time from capsule ingestion to expulsion. Regional transit times (stomach, small bowel, colon) were also recorded. The 3D-Transit recording was initiated on day four in each condition. After 6 h of fasting, participants received a small standardized meal (285 kcal) with a glass of water and swallowed the 3D-transit capsule immediately afterwards. Participants fasted for an additional 6 h upon ingesting the capsule. In order to track the capsule, participants wore sensors fitted in an elastic belt around the abdomen for six days. Data was assessed on day 11 to ensure that the capsule was expelled. If any doubt of expulsion was present, participants were asked to undergo an abdominal X-ray.

**PAC-SYM:** The 'Patient Assessment of Constipation-Symptoms' (PAC-SYM), a 12-item questionnaire assessing subjective GI symptoms, has good internal consistency and test-retest reliability ( $\alpha=0.89$ ;  $r=0.75$ ) [18]. Each item, e.g., "Bowel movements that were too hard", is rated on a 5-point Likert scale from 0 to 4 (0 = absence of symptoms; 4 = very severe symptoms). A total score was calculated by dividing the sum score with number of completed items, with a possible range of 0–4, where higher scores indicate higher symptom severity. Participants filled in the PAC-SYM questionnaire once every day (14 days throughout each condition). A total PAC-SYM score was calculated as an average score across days four to 14 for each condition as OIC in



**Figure 1:** Procedure for each treatment period. Abbreviations: PAC-SYM = Patient Assessment of Constipation-Symptoms Scale; SSAS = Somatosensory Amplification Scale; GITT = Gastrointestinal Transit Time.

experimental studies usually starts about four days after treatment start [19, 20].

### Blinding assessment

To check whether participant blinding was successful, participants were asked at the beginning (day 1) and end (day 14) of each treatment period to guess whether they had received active or placebo treatment.

### Psychological factors

**Neuroticism:** Neuroticism was assessed with the 8-item neuroticism subscale of the ‘Big Five Inventory’ (BFI), which has good internal consistency and reliability ( $\alpha=0.83$ ;  $r=0.75$ ) [21]. Each item, e.g., “*I see myself as someone who can be tense*”, is rated on a 5-point scale from 1 to 5 (1 = disagree strongly; 5 = agree strongly).

**Pain catastrophizing:** The ‘Pain Catastrophizing Scale’ (PCS) is a 13-item questionnaire assessing rumination, magnification, and helplessness in the context of pain with good internal consistency ( $\alpha=0.87$ ) [22]. Each item, e.g., “*I keep thinking about how much it hurts*”, is rated on a 5-point scale from 0 to 4 (0 = not at all; 4 = all the time).

**Somatosensory amplification:** The ‘Somatosensory Amplification Scale’ (SSAS), a 10-item questionnaire assessing sensitivity to normal somatic and visceral sensations, has good internal consistency and test-retest reliability in outpatients ( $\alpha=0.77$ ;  $r=0.87$ ) [23]. Each item, e.g., “*I am quick to sense the hunger contractions in my stomach*”, is rated on a 5-point scale from 1 to 5 (1 = not at all true; 5 = extremely true).

### Statistical analysis

Statistical analyses were performed in SPSS 26. One-way repeated measures ANOVAs were carried out to check the effect of treatment on objective and subjective measures of constipation (GI transit times and PAC-SYM scores, respectively). Pearson’s and Spearman’s correlation analyses were carried out for parametric and non-parametric data, respectively, to investigate the association between GI transit times and PAC-SYM scores. Bonferroni corrections were applied to control for familywise error. The same correlation analyses were carried out to test the association between psychological traits (neuroticism, pain catastrophizing, somatosensory amplification), and PAC-SYM scores and GI transit times. For significant correlations, simple linear

regression analyses were carried out to investigate predictive associations between subjective OIC, objective OIC, and psychological traits. Participant blinding (pre- and post-treatment) was assessed with Fisher’s Exact Tests.  $p<0.05$  was considered significant.

## Results

Twenty-one healthy male subjects completed the study. Mean age was  $24.9 \pm 2.7$  (SD) years, and mean body mass index was  $25.3 \pm 2.5$  kg/m<sup>2</sup>.

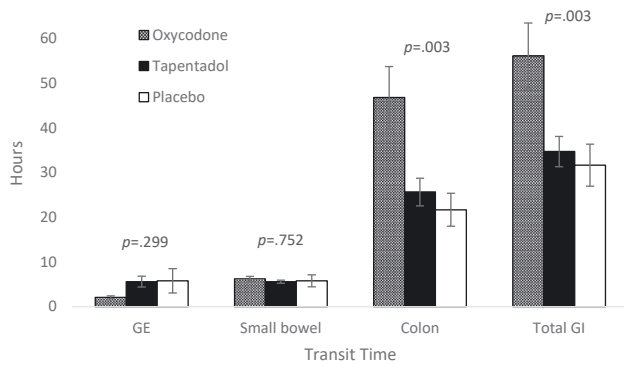
### Manipulation check: opioid-induced constipation

#### GI transit time

Detailed results on the effect of treatment on GI transit times are published elsewhere [15]. Here, the results are summarized in Figure 2. Oxycodone significantly increased total GI transit time compared to placebo, but the difference in total GI transit time between oxycodone and tapentadol did not reach statistical significance. Of the regional transit times, oxycodone significantly increased colon transit time compared to tapentadol and placebo. There were no treatment effects on gastric emptying or small bowel transit time. Therefore, only total GI and colonic transit times were included in subsequent analyses.

#### PAC-SYM score

No baseline differences were found in mean PAC-SYM score between the three conditions. There was a significant effect of treatment on PAC-SYM score,  $F(1.2,24.5)=13.4$ ,  $p=0.001$ ,  $\eta^2_p=0.401$  (Figure 3). A post hoc analysis showed that oxycodone significantly increased subjective experience of constipation compared to tapentadol ( $p=0.007$ ) and placebo ( $p=0.001$ ).



**Figure 2:** Treatment effect on gastrointestinal transit times. Abbreviations: GI = Gastrointestinal; GE = Gastric Emptying.

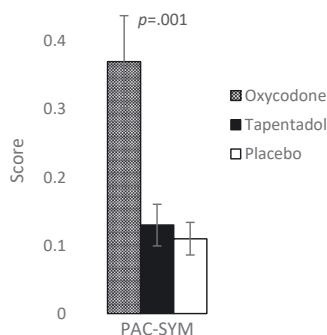
### Aim 1: association between subjective and objective measures of OIC

PAC-SYM score was strongly associated with total GI transit time ( $r=0.676$ ,  $p(\text{adjusted})=0.006$ ) and colonic transit time ( $r=0.627$ ,  $p(\text{adjusted})=0.024$ ) in the oxycodone arm (Table 1). No significant correlations emerged between PAC-SYM score and total GI or colonic transit times in the tapentadol and placebo arms.

In the oxycodone arm, PAC-SYM score significantly predicted total GI transit time ( $b=52.8$ ,  $t(17)=5.43$ ,  $p<0.001$ ), explaining 43% of the variance (adjusted  $R^2=0.425$ ,  $F(1,17)=14.29$ ,  $p=0.001$ ). Similarly, PAC-SYM score significantly predicted colonic transit time ( $b=46.8$ ,  $t(17)=4.47$ ,  $p<0.001$ ), explaining 36% of the variance (adjusted  $R^2=0.358$ ,  $F(1,17)=11.03$ ,  $p=0.004$ ).

### Aim 2: blinding success

For treatment guesses at baseline (Table 2), most participants could not guess which treatment they had just



**Figure 3:** Treatment effect on Patient Assessment of Constipation-Symptoms score. Abbreviations: PAC-SYM = Patient Assessment of Constipation-Symptoms.

started. For post-treatment guesses, all, but one participant, correctly guessed that they had received active treatment after receiving oxycodone ( $p<0.001$ ). However post-tapentadol and -placebo treatment, comparable amounts of participants guessed that they had received active and placebo treatment. Participant blinding was violated only in the oxycodone condition post-treatment.

### Aim 3: association between OIC and psychological factors

After Bonferroni correction, there were no significant associations between OIC measures (PAC-SYM, GI transit times) and neuroticism, pain catastrophizing, or somatosensory amplification, although moderate effect sizes emerged (Table 3).

## Discussion

This study found a strong association between objective measures and the subjective experience of OIC when participants were treated with oxycodone. Furthermore, participants were able to guess that they had received active treatment when treated with oxycodone, hinting that expectations could play a role in the subjective experience of OIC. Finally, some patterns of associations between OIC and other psychological factors emerged, although none reached significance.

### Subjective and objective measures of OIC

There was a strong association between the subjective and objective measures of constipation in the oxycodone condition, but no associations were found in neither the tapentadol nor the placebo conditions. In contrast, previous studies have found no associations between subjective and objective measures of oxycodone-induced constipation [3–8]. Oxycodone treatment in the current study prolonged total GI transit with an additional 11 h compared to previous studies using the same methodology [6, 24], which might be explained by increased treatment duration (4–5 vs. 14 days). Our results may therefore more closely mimic OIC in clinical practice, and constipation may simply need to reach a certain level of severity before the subjective experience reflects objective measures of constipation. Clinical studies nonetheless find no associations between subjective and objective measures of constipation, but this may be due to confounding factors that

**Table 1:** Correlation coefficients between subjective and objective measures of constipation.

|                       | PAC-SYM score           |                    |                                       |                         |                    |                                       |                         |                    |                                       |
|-----------------------|-------------------------|--------------------|---------------------------------------|-------------------------|--------------------|---------------------------------------|-------------------------|--------------------|---------------------------------------|
|                       | Oxycodone               |                    |                                       | Tapentadol              |                    |                                       | Placebo                 |                    |                                       |
|                       | Correlation coefficient | Unadjusted p-Value | Bonferroni-based p-Value <sup>a</sup> | Correlation coefficient | Unadjusted p-Value | Bonferroni-based p-Value <sup>a</sup> | Correlation coefficient | Unadjusted p-Value | Bonferroni-based p-Value <sup>a</sup> |
| Total GI transit time | $r=0.676^*$             | 0.001              | 0.006                                 | $r_s=0.318$             | 0.184              | 1.000                                 | $r_s=0.153$             | 0.558              | 1.000                                 |
| Colonic transit time  | $r=0.627^*$             | 0.004              | 0.024                                 | $r_s=0.193$             | 0.428              | 1.000                                 | $r_s=0.364$             | 0.151              | 0.906                                 |

<sup>a</sup>Adjusted p-value significant at 0.05-level. \* $p<0.05$  after Bonferroni correction. GI, gastrointestinal; PAC-SYM, patient assessment of constipation-symptoms scale;  $r$ , Pearson's  $r$ ;  $r_s$ , Spearman's  $\rho$ .

**Table 2:** Test of blinding; actual treatment by guessed treatment at baseline and post-treatment.

| Actual treatment                 | Test of blinding             |         |            |                          |         |            |
|----------------------------------|------------------------------|---------|------------|--------------------------|---------|------------|
|                                  | Guessed treatment (baseline) |         |            | Guessed treatment (post) |         |            |
|                                  | Active                       | Placebo | Don't know | Active                   | Placebo | Don't know |
| Oxycodone                        | 9                            | 0       | 12         | 20                       | 0       | 1          |
| Tapentadol                       | 5                            | 1       | 15         | 10                       | 10      | 1          |
| Placebo                          | 7                            | 1       | 13         | 7                        | 10      | 4          |
| Fisher's exact test <sup>a</sup> | 2.73, $p=0.702$              |         |            | 22.7, $p<0.001$          |         |            |

<sup>a</sup>Two-tailed.

**Table 3:** Correlation coefficients between measures of constipation and psychological factors in the context of oxycodone.

|            | Neuroticism             |                    |                                       | Pain catastrophizing    |                    |                                       | Somatosensory amplification |                    |                                       |
|------------|-------------------------|--------------------|---------------------------------------|-------------------------|--------------------|---------------------------------------|-----------------------------|--------------------|---------------------------------------|
|            | Correlation coefficient | Unadjusted p-Value | Bonferroni-based p-Value <sup>a</sup> | Correlation coefficient | Unadjusted p-Value | Bonferroni-based p-Value <sup>a</sup> | Correlation coefficient     | Unadjusted p-Value | Bonferroni-based p-Value <sup>a</sup> |
| Total GITT | $r_s=0.057$             | 0.817              | 1.000                                 | $r_s=0.138$             | 0.572              | 1.000                                 | $r_s=0.311$                 | 0.195              | 1.000                                 |
| Colonic TT | $r_s=0.016$             | 0.948              | 1.000                                 | $r_s=0.130$             | 0.595              | 1.000                                 | $r_s=0.282$                 | 0.243              | 1.000                                 |
| PAC-SYM    | $r_s=0.390$             | 0.081              | 0.729                                 | $r_s=0.279$             | 0.221              | 1.000                                 | $r_s=0.491$                 | 0.024              | 0.216                                 |

<sup>a</sup>Adjusted p-value significant at 0.05-level. GITT, gastrointestinal transit time; TT, transit time; PAC-SYM, patient assessment of constipation-symptoms scale;  $r$ , Pearson's  $r$ ;  $r_s$ , Spearman's  $\rho$ .

are avoided using healthy volunteers and experimentally induced constipation. This study shows that we now have a good OIC model in healthy subjects in which we can investigate the influence of confounders that would typically emerge in clinical practice, for example the influence of psychological traits.

## Blinding and OIC

Expectations may also play a role in OIC. In the current study, only in the oxycodone condition did participants correctly guess that they were receiving active treatment, and oxycodone had the largest effect on subjective and objective



measures of constipation. Furthermore, it was the only condition in which subjective and objective measures correlated. The severity of bowel symptoms induced by the oxycodone treatment may have made participants aware that they were receiving active treatment. Consecutively, the awareness of receiving active treatment may have influenced expectations of, and subjective experience of, bowel symptoms. Evidence from hypnotherapy and open-label placebo trials suggests that expectations influence bowel symptoms [25, 26], which is further supported by research on the brain-gut connections. Since treatment-guess was only assessed pre and post treatment, it is unknown how early in the oxycodone treatment condition participants became aware that they were receiving active treatment. Yet, as previous studies have shown a self-reinforcing relationship between expectations and pain in irritable bowel syndrome [27], a regulation loop may exist, in which GI transit time influence treatment expectations and subjective experience of constipation, which in turn may increase GI transit times further. These tentative results warrant further investigation into the influence of expectations on OIC as this could have important clinical consequences. Furthermore, it highlights the importance of assessing blinding success to aid interpretation of results.

## Psychological factors and OIC

Although subjective and objective measures of OIC were not significantly associated with the psychological factors neuroticism, pain catastrophizing and somatosensory amplification in this study, interesting patterns of moderate effect sizes emerged especially related to the subjective experience of constipation. The current study was exploratory in nature but the tentative indications that psychological factors may play a role in OIC warrant further investigation of the association between psychological factors and OIC in larger samples.

## Implications and conclusion

A good experimental model of OIC has been established in healthy participants in which subjective and objective measures of constipation are highly linked. Results indicate that treatment expectations could play an important role in the subjective experience of OIC, and support the importance of assessment of blinding success in study trials. Besides expectations, other psychological factors may be associated with OIC, but studies in clinical settings and with larger sample sizes are needed to investigate this further. Further exploration of associations between

expectations, psychological factors and OIC may benefit clinical practice, enabling clinicians to tailor treatment plans to each individual patient.

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**Author contributions:** All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

**Competing interests:** Authors state no conflict of interest.

**Informed consent:** Informed consent has been obtained from all individuals included in this study.

**Ethical approval:** Research involving human subjects complied with all relevant national regulations and institutional policies and has been approved by the North Denmark Region Committee on Health Research Ethics and the Danish Health and Medicines Authority (reference numbers: N-20170009 and 2017041794).

## References

1. Farmer AD, Drewes AM, Chiarioni G, De Giorgio R, O'Brien T, Morlion B, et al. Pathophysiology and management of opioid-induced constipation: European expert consensus statement. *United European Gastroenterol J* 2019;7:7–20.
2. Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, et al. Opioid complications and side effects. *Pain Physician* 2008;11:S105–20.
3. Cowlam S, Vinayagam R, Khan U, Marsden S, Minty I, Moncur P, et al. Blinded comparison of faecal loading on plain radiography versus radio-opaque marker transit studies in the assessment of constipation. *Clin Radiol* 2008;63:1326–31.
4. Grotz RL, Pemberton JH, Talley NJ, Rath DM, Zinsmeister AR. Discriminant value of psychological distress, symptom profiles, and segmental colonic dysfunction in outpatients with severe idiopathic constipation. *Gut* 1994;35:798–802.
5. Knudsen K, Krogh K, Østergaard K, Borghammer P. Constipation in Parkinson's disease: subjective symptoms, objective markers, and new perspectives. *Mov Disord* 2017;32:94–105.
6. Poulsen JL, Nilsson M, Brock C, Sandberg TH, Krogh K, Drewes AM. The impact of opioid treatment on regional gastrointestinal transit. *J Neurogastroenterol Motil* 2016;22:282–91.
7. Nilsson M, Poulsen JL, Brock C, Sandberg TH, Gram M, Frøkjær JB, et al. Opioid-induced bowel dysfunction in healthy volunteers assessed with questionnaires and MRI. *Eur J Gastroenterol Hepatol* 2016;28:514–24.
8. Grønlund D, Vase L, Knudsen SA, Christensen M, Drewes AM, Olesen AE. Comparison of subjective and objective measures of constipation – employing a new method for categorizing gastrointestinal symptoms. *J Pharmacol Toxicol Methods* 2018; 94:23–8.

9. Hróbjartsson A, Forfang E, Haahr M, Als-Nielsen B, Brorson S. Blinded trials taken to the test: an analysis of randomized clinical trials that report tests for the success of blinding. *Int J Epidemiol* 2007;36:654–63.
10. Hróbjartsson A, Emanuelsson F, Skou Thomsen AS, Hilden J, Brorson S. Bias due to lack of patient blinding in clinical trials. A systematic review of trials randomizing patients to blind and nonblind sub-studies. *Int J Epidemiol* 2014;43:1272–83.
11. Howick J, Webster R, Kirby N, Hood K. Rapid overview of systematic reviews of placebo effects reported by patients taking placebos in clinical trials. *Trials* 2018;19:674.
12. Jones MP, Wessinger S, Crowell MD. Coping strategies and interpersonal support in patients with irritable bowel syndrome and inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2006;4:474–81.
13. Hazlett-Stevens H, Craske MG, Mayer EA, Chang L, Naliboff BD. Prevalence of irritable bowel syndrome among university students: the roles of worry, neuroticism, anxiety sensitivity and visceral anxiety. *J Psychosom Res* 2003;55:501–5.
14. Lackner JM, Quigley BM. Pain catastrophizing mediates the relationship between worry and pain suffering in patients with irritable bowel syndrome. *Behav Res Ther* 2005;43:943–57.
15. Mark EB, Nedergaard RB, Hansen TM, Nissen TD, Frøkjær JB, Scott SM, et al. Tapentadol results in less deterioration of gastrointestinal function and symptoms than standard opioid therapy in healthy male volunteers. *Neurogastroenterol Motil* 2021; e14131. <https://doi.org/10.1111/nmo.14131> [Epub ahead of print].
16. Meng Z, Yu J, Acuff M, Luo C, Wang S, Yu L, et al. Tolerability of opioid analgesia for chronic pain: a network meta-analysis. *Sci Rep* 2017;7:1995.
17. Haase AM, Gregersen T, Schlageter V, Scott MS, Demierre M, Kucera P, et al. Pilot study trialling a new ambulatory method for the clinical assessment of regional gastrointestinal transit using multiple electromagnetic capsules. *Neuro Gastroenterol Motil* 2014;26:1783–91.
18. Frank L, Kleinman L, Farup C, Taylor L, Miner P Jr. Psychometric validation of a constipation symptom assessment questionnaire. *Scand J Gastroenterol* 1999;34:870–7.
19. Poulsen JL, Mark EB, Brock C, Frøkjær JB, Krogh K, Drewes AM. Colorectal transit and volume during treatment with prolonged-release oxycodone/naloxone versus oxycodone plus macrogol 3350. *J Neurogastroenterol Motil* 2018;24: 119–27.
20. Grønlund D, Poulsen JL, Krogh K, Brock C, Liao D, Gregersen H, et al. The impact of naloxegol on anal sphincter function – using a human experimental model of opioid-induced bowel dysfunction. *Eur J Pharm Sci* 2018;117:187–92.
21. John OP, Srivastava S. The big five taxonomy: history, measurement, and theoretical perspectives. In: Pervin L, John OP, editors. *Handbook of personality: theory and research*, 2nd ed. New York: Guilford; 1999:102–38 pp.
22. Sullivan MJ, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. *Psychol Assess* 1995;7. <https://doi.org/10.1037/1040-3590.7.4.524>.
23. Speckens AEM, Spinhoven P, Sloekers PPA, Bolk JH, van Hemert AM. A validation study of the whitely index, the illness attitude scales, and the somatosensory amplification scale in general medical and general practice patients. *J Psychosom Res* 1996;40: 95–104.
24. Olesen AE, Grønlund D, Mark EB, Krogh K, Frøkjær JB, Drewes AM. Effects of naloxegol on gastrointestinal transit and colonic fecal volume in healthy participants receiving oxycodone. *J Neurogastroenterol Motil* 2019;25:602–10.
25. Lindfors P, Unge P, Arvidsson P, Nyhlin H, Björnsson E, Abrahamsson H, et al. Effects of gut-directed hypnotherapy on IBS in different clinical settings—results from two randomized, controlled trials. *Off J Am Coll Gastroenterol|ACG* 2012;107. <https://doi.org/10.1038/ajg.2011.340>.
26. Kaptchuk TJ, Friedlander E, Kelley JM, Sanchez MN, Kokkotou E, Singer JP, et al. Placebos without deception: a randomized controlled trial in irritable bowel syndrome. *PLoS One* 2010;5: e15591.
27. Vase L, Robinson ME, Verne GN, Price DD. Increased placebo analgesia over time in irritable bowel syndrome (IBS) patients is associated with desire and expectation but not endogenous opioid mechanisms. *Pain* 2005;115:338–47.