Effects of opium tincture on the enteric and central nervous systems

A randomized controlled trial

Okdahl, Tina; Mark, Esben Bolvig; Nedergaard, Rasmus Bach; Knoph, Cecilie Siggaard; Cook, Mathias Ellgaard; Krogh, Klaus; Drewes, Asbjørn Mohr

Published in:
Basic & Clinical Pharmacology & Toxicology

DOI (link to publication from Publisher):
10.1111/bcpt.13850

Publication date:
2023

Document Version
Publisher's PDF, also known as Version of record

Received: 23 January 2023 | Revised: 16 February 2023 | Accepted: 23 February 2023

DOI: 10.1111/bcpt.13850

ORIGINAL ARTICLE

BCPT Basic & Clinical Pharmacology & Toxicology

Effects of opium tincture on the enteric and central nervous systems: A randomized controlled trial

Tina Okdahl[1] | **Esben Bolvig Mark**[1,2] | **Rasmus Bach Nedergaard**[1] | **Cecilie Siggaard Knoph**[1,2] | **Mathias Ellgaard Cook**[1,2] | **Klaus Krogh**[3] | **Asbjørn Mohr Drewes**[1,2]

[1]Mech-Sense, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Aalborg, Denmark

[2]Clinical Institute, Aalborg University, Aalborg, Denmark

[3]Neurogastroenterology Unit, Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark

Correspondence
Asbjørn Mohr Drewes, Mech-Sense, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Mølleparkvej, DK-9000 Aalborg, Denmark.
Email: amd@rn.dk

Funding information
Pharmanovia, Grant/Award Number: Unresticted grant

Abstract

Opioids change gut motility, and opium tincture has been used for treatment of chronic diarrhoea for centuries. However, the effects have never been documented in controlled trials. We aimed to investigate the effects of opium tincture on gastrointestinal transit and motility, frequency of bowel movements, stool consistency, gastrointestinal symptoms and sedation. Twenty healthy subjects were included in this randomized controlled trial. Opium tincture or placebo was each applied for 9 days. Gastrointestinal transit and motility were investigated with the 3D-transit system. Bowel movements and gastrointestinal symptoms were recorded daily. General cognition, reaction time, memory and electroencephalography were used to assess effects on the central nervous system. Opium tincture doubled colonic transit (49 vs. 23 h, $p < 0.001$), decreased antegrade colonic movements ($p < 0.05$), reduced daily bowel movements (0.7 vs. 1.2, $p < 0.001$) and increased stool consistency (Type 3 vs. Type 4, $p < 0.001$). No changes in general cognition, reaction time or memory were observed, and minor changes of power observed by electroencephalography did not indicate sedation. This study is the first to show that opium tincture has anti-propulsive properties in the healthy gut, while no sedative effects were seen. This indicates that opium tincture is a relevant and safe treatment option in chronic diarrhoea.

KEYWORDS
diarrhoea, gastrointestinal transit, motility, opium tincture

1 | INTRODUCTION AND BACKGROUND

Opioids possess potent gastrointestinal properties, evident by the fact that 50%–80% of chronic pain patients on opioid therapy for analgesic purposes develop

Trial registration number: NCT05702190.

opioid-induced constipation.[1,2] The physiological background for this adverse reaction is well-described as an overall inhibitory effect of both endogenous and exogenous opioids on gastrointestinal motility and secretion as well as sphincter function mediated via μ-opioid receptors within the enteric nervous system resulting in, for example, prolongation of colonic transit.[3–6] These anti-propulsive actions can be applied for treatment of chronic idiopathic diarrhoea, in which gastrointestinal motility as well as secretion of water across the interstitial wall are increased.[7] As such, these effects of opioids have been used as treatment of diarrhoea for centuries in addition to its pain-relieving properties.[8] Since the 1970s, the opioid receptor agonist loperamide, displaying limited ability to cross the blood-brain barrier, has been widely prescribed for the treatment of diarrhoea. Loperamide is now considered first-line choice for treatment of chronic idiopathic diarrhoea.[7] Despite this, very little evidence exists regarding the mechanistic actions of this drug on gastrointestinal function as well as its superiority as an anti-propulsive agent over other opioids. Opium tincture, consisting of raw opium derived from *Papaver somniferum* dissolved in ethanol, has been marketed as an antidiarrhoeal drug since the eighteenth century.[9] Today, it is used as symptomatic treatment of chronic idiopathic diarrhoea refractory to first-line choices such as loperamide. Despite the application of opium tincture in modern medicine, no clinical studies have investigated its effect on gastrointestinal function. Moreover, clinicians may be reluctant in prescribing opium tincture for chronic diarrhoea due to insufficient knowledge regarding sedative effects as well as risk of addiction and abuse.

Taken together, there is a substantial knowledge gap regarding the effect and safety of opioid tincture in antidiarrhoeal treatment. Thus, both efficacy studies in chronic diarrhoea patients and mechanistic studies in healthy volunteers free from confounders such as comorbidities and co-medication are warranted. With the present study in healthy volunteers, we wish to provide evidence-based insights into the effects of opium tincture on gastrointestinal function, which until now has been anecdotal. We hypothesized that opium tincture inhibits gastrointestinal transit and motility, while effects on the central nervous system are limited. Thus, the primary aim of the study was to investigate effects on gastrointestinal transit times, while secondary aims included evaluation of gastrointestinal motility patterns, frequency of bowel movements, consistency of stools and other gastrointestinal symptoms. In addition, the potential sedative properties of opium tincture were investigated as a tertiary aim.

2 | MATERIALS AND METHODS

2.1 | Study overview and population

The study was designed as a randomized, double-blind, placebo-controlled cross-over trial, in which 20 healthy subjects received opium tincture (Dropizol®, Pharmanovia, Denmark) or placebo (Glostrup Pharmacy, Glostrup, Denmark) for 9 days during two identical study periods separated by at least 28 days of wash-out. An overview of study periods is provided in Figure 1. Included subjects were all opioid-naïve (short-term opioid therapy for acute

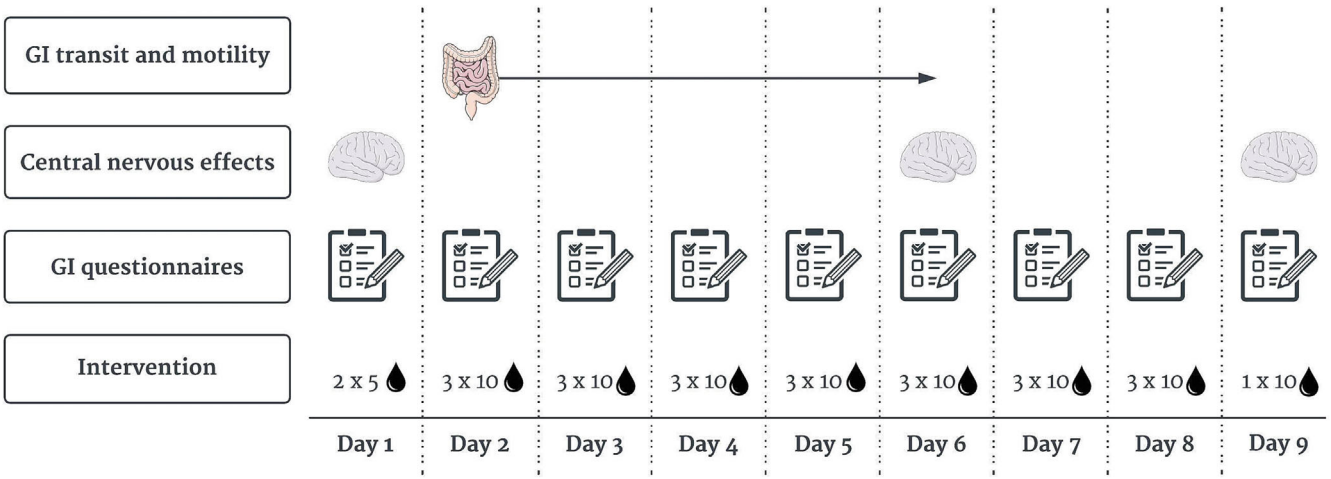

FIGURE 1 Study period overview. Gastrointestinal (GI) transit and motility was measured by 3D-transit system. Tests of central nervous effects included pupillometry, continuous reaction time, digit span test, Mini-Mental State Examination and electroencephalography (not performed on Day 6). GI questionnaires included Bristol Stool Form Scale, Patient Assessment of Constipation Symptoms and Gastrointestinal Symptom Rating Scale. The intervention was either opium tincture or placebo.

pain more than 5 years prior to inclusion was allowed). Exclusion criteria included history of major psychiatric illness, prior or current substance abuse and medicine known to affect gastrointestinal motility. The study was powered to detect a minimal increase in whole gut transit time of 6 ± 6 h between active and placebo treatment with a power of 80% and a two-sided significance level of 0.05. Randomization was performed by Glostrup Pharmacy, Glostrup, Denmark. Subjects, study personnel and data analysts were all blinded to the allocation. Opium tincture or placebo was self-administered as 2 × 5 drops on Day 1, 3 × 10 drops on Days 2–8 and 1 × 10 drops on Day 9 in each study period. Dropizol® contains raw opium, ethanol (33% v/v) and purified water. The maximum daily dosage in this study of 30 drops corresponds to 15 mg of oral morphine. Compliance was monitored by asking subjects to note the time and number of ingested drops of each self-administration in a daily drug diary. Furthermore, returned vials were weighed to verify that the self-administration of drops was in accordance with diary notes. The placebo consisted of barley malt extract, ethanol (33% v/v) and purified water. The investigational product and placebo were identical in appearance and taste. Subjects were inquired about any adverse events at the end of both study periods. Causality with the investigational product was assessed by a medical doctor. The study was carried out at Aalborg University Hospital, Aalborg, Denmark from March 2021 to June 2022. All subjects signed an informed consent form before inclusion in the study. The study protocol and amendments were approved by The North Denmark Region Committee on Health Research Ethics (N-20200102) and by the Danish Health and Medicines Authority (EudraCT No.: 2020-004875-41). The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines and was monitored by the Good Clinical Practice (GCP) unit at Aalborg University Hospital. Furthermore, the study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies.[10]

2.2 | Effects of opioid tincture on the gastrointestinal tract

2.2.1 | Gastrointestinal transit times

Gastrointestinal transit times were measured with the 3D-transit electromagnetic capsule system (Motilis Medica SA, Lausanne, Switzerland), which has been described in detail earlier.[11] Subjects ingested an electromagnetic capsule on Day 2 of each treatment period and were instructed to wear an external detector the following 4 days while noting the time and date of each bowel movement. Capsule position and rotation were detected with a frequency of 10 Hz and afterwards analysed to estimate passage from the stomach to duodenum and from ileum to caecum. This information identified gastrointestinal transit times for the stomach, small bowel and colon. Additionally, the colonic transit was subdivided into four segments (ascending, transverse, descending and rectosigmoid colon). Whole gut transit time was calculated as the time between the ingestion and expulsion of the capsule. Expulsion time was defined as the time of capsule signal loss. The expulsion time point was verified by subject diaries of bowel movements during study periods.

2.2.2 | Detailed colonic motility measurements

3D-transit recordings were also used to extract data regarding detailed colonic motility. Specific movements of the capsule were identified and sub-grouped into four distinct patterns: long, fast antegrade movements (distance: >10 cm; velocity: >10 cm/min), fast antegrade movements (distance: >4 and <10 cm; velocity: >4 cm/min), slow antegrade movements (distance: >4 cm; velocity: <4 cm/min and >4 cm/h) and slow retrograde movements (retrograde distance: <4 cm; velocity: <4 cm/min and >4 cm/h) based on previously published thresholds.[12] The analysis was performed using MATLAB (version R2021a, MathWorks Inc.). A representative example of colonic progression patterns in one subject during active and placebo treatment is provided in Figure 2.

2.2.3 | Spontaneous bowel movements and stool consistency

Subjects were asked to fill out Bristol Stool Form Scale after each bowel movement in both study periods for classification of stool type in seven types ranging from 1 (separate hard lumps) to 7 (watery and no solid pieces). A Bristol Stool Form Scale type of 3 or 4 is considered normal, while 1–2 indicates constipation, and 5–7 indicates diarrhoea.[13] Additionally, number of daily bowel movements was registered by subjects, and a total mean of each study period was calculated.

2.2.4 | Gastrointestinal symptoms

During both treatment periods, subjects completed a daily online survey consisting of two validated

questionnaires measuring gastrointestinal symptoms: the Gastrointestinal Symptom Rating Scale (GSRS) and Patient Assessment of Constipation Symptoms (PAC-SYM).[14,15] The GSRS is a disease-specific questionnaire developed to evaluate various gastrointestinal symptoms. It contains 15 items assigned to five subdomains: reflux (two items), abdominal pain (three items), indigestion (four items), diarrhoea (three items) and constipation (three items). Each item is rated on a 7-point Likert scale (0: *no discomfort*; 1: *minor discomfort*; 2: *mild discomfort*; 3: *moderate discomfort*; 4: *moderately severe discomfort*; 5: *severe discomfort*; and 6: *very severe discomfort*).[14] The PAC-SYM is a sensitive and reliable instrument for monitoring symptoms of constipation. It contains 12 items assigned to three subdomains: abdominal-related symptoms (four items), rectal-related symptoms (three items) and stool-related symptoms (five items). Each item is rated on a 5-point Likert scale (0: *symptom absent*, 1: *mild*, 2: *moderate*, 3: *severe* and 4: *very severe*).[15] A global mean score was calculated for each questionnaire as well as a mean score for each subdomain. At baseline, the recall period was 48 h, and 24 h at the remaining timepoints.

2.3 | Effects of opioid tincture on the central nervous system

2.3.1 | Mini-Mental State Examination

General cognition was evaluated using the Mini-Mental State Examination, which covers several domains of cognitive function.[16] A maximum score of 30 points is achieved by correctly answering tests regarding

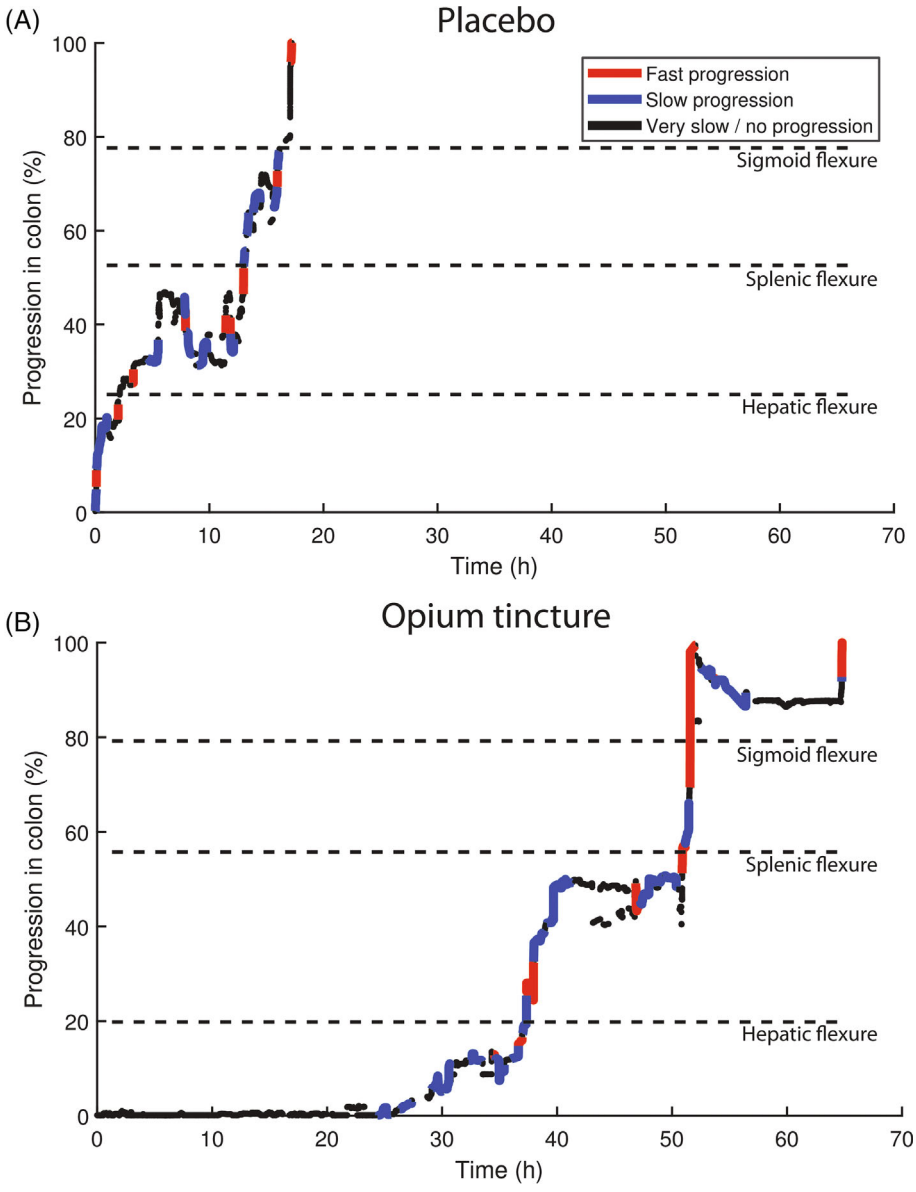

FIGURE 2 Progression patterns in the colon during treatment with placebo (A) and opium tincture (B) in the same subject. Progression of the 3D-transit capsule from cecum (0%) to rectum (100%) is represented on the y-axis.

orientation to time and place (10 points), word registration (3 points), attention and calculation (5 points), word recall (3 points), language (8 points) and visual construction (1 point). The Mini-Mental State Examination was applied at baseline, Day 6 and Day 9 in both study periods.

2.3.2 | Continuous reaction time

For assessment of attention and vigilance, a continuous reaction time measurement was performed using EKHO software (Bitmatic, Aarhus, Denmark). The continuous reaction time test has previously been validated as a measure of cognitive function in healthy subjects.[17] During the test, subjects were placed in a quiet room with no visual distraction. A total of 150 auditory signals of 500 Hz tones at 90 dB were provided via headphones with external sound blocking at random intervals (2–6 s). Subjects were instructed to respond to the signal by pressing a handheld button as fast as possible. Scores of the 10th (fastest), 50th (median) and 90th (slowest) percentile of reaction times (measured in milliseconds) were provided by the software along with a continuous reaction time index calculated as 50th percentile / (90th percentile – 10th percentile). The index reflects the stability in reaction times, with a low index value representing large intrapersonal variation.[18] Continuous reaction time was investigated at baseline, Day 6 and Day 9 in both study periods.

2.3.3 | Digit span test

The digit span test was applied for evaluation of concentration as well as working and short-term memory.[19,20] An online tool (https://timodenk.com/blog/digit-span-test-online-tool/) was used for this purpose. The subjects were instructed to remember and recall a sequence of digits in increasing length. Digits were presented visually with one digit per second. Two tests were performed in both forward and reverse order at baseline, Day 6 and Day 9, and number of correctly remembered digits was recorded.

2.3.4 | Pupil diameter

Pupil diameter was used as an objective measure of central effects of opium tincture as opioids are known to induce miosis when present in the central nervous system.[21] A digital handheld device (PLR®-3000, NeuroOptics, USA) was used for the measurements at baseline, Day 6 and Day 9. A minimum of 5 min of dimmed light preceded each recording. The mean pupil size from consecutive recordings on the right and left eye was used in the data analysis.

2.3.5 | Electroencephalography (EEG)

The effects of opium tincture on the cortex were investigated using EEG in a resting state for 5 min at baseline and Day 9. EEG was recorded from a 34-channel cap (36ch prewired cylindrical Ag/AgCl electrodes, QuickCap International, Neuroscan) and amplified on a NuAmp system (NuAmp, Neuroscan, El Paso, TX, USA). Electrode gel was applied in each recording channel to reduce the electrode impedance below 5 kΩ, and the sampling frequency was 1000 Hz. Subjects were seated in a comfortable incline position and instructed to sit quietly with closed eyes, without sleeping, while minimizing eye movement during the recording.

All preprocessing was performed in Matlab R2021b and eeglab v.2002.0. Electrodes not recording brain waves were removed from the data set. The data were bandpass filtered between 1 and 70 Hz with a notch filter between 49 and 51 Hz, line noise was removed using cleanLineNoise (v2.00) from the eeglab toolbox, and artefact subspace reconstruction was used to remove additional noise. Missing channels were then interpolated using spherical interpolation. Independent component analysis was used to identify noise and artefacts aided by ICLabel v1.3.[22] All independent components were manually investigated.

For spectral analysis, the frequency bands delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz) and beta (12–32 Hz) were analysed using a complex Morlet wavelet. The wavelet had a centre frequency of 1 with a bandwidth of 10 Hz and a between-scale frequency resolution of 0.5 Hz. Five brain regions were extracted (frontal, temporal left, temporal right, central and occipital) for data analysis.

2.4 | Statistics

For gastrointestinal transit times, data were compared using a repeated measures mixed model with treatment (placebo and opium tincture) and gastrointestinal segments (stomach, small bowel and colon) as factors. Detailed colonic transit and motility were analysed using the same mixed model type with treatment (placebo and opium tincture) and colonic segments (ascending colon, transverse colon, descending colon and rectosigmoid colon) as factors. Differences in number of motility

patterns per hour between treatments were investigated by Wilcoxon matched-pairs signed-rank test. Bowel movement consistency was analysed by a repeated measures mixed model with treatment (opium tincture and placebo) and days (Days 2–8) as factors. Distribution of mean daily bowel movements between treatments was evaluated by visual inspection of histograms and by the Shapiro–Wilks test of normality and subsequently compared by a paired samples *t*-test. For analyses of questionnaire scores, Mini-Mental State Examination scores, continuous reaction time measures and digit span data, the same mixed model was applied with treatment (placebo and opium tincture) and days (Days 1, 6 and 9) as factors. For EEG data, the baseline measures were subtracted from the post-treatment measures and investigated using repeated measures mixed model with treatments (placebo and opium tincture) and brain regions (frontal, central, temporal left, temporal right and occipital) as factors. The data were analysed independently for each frequency band. In all cases of significant findings, a subsequent Bonferroni-corrected post hoc analysis accounting for multiple comparisons was performed. Data are presented as mean ± standard deviation or median (interquartile range) based on data distribution evaluated by Shapiro–Wilks test of normality. An α-level below 0.05 was considered significant in all analyses.

3 | RESULTS

3.1 | Study population

A total of 26 subjects were screened for eligibility, and of these, 20 were included in the study. During the study, two subjects were excluded due to noncompliance with the protocol and were subsequently replaced by mirror-randomized new subjects (Figure 3). Data collected from excluded subjects were not included in the analysis. Median age of the 20 subjects, who completed the study, was 24 years (range 20–72 years), and median BMI was 23 kg/m^2 (range 19–37 kg/m^2). The distribution of sex in the study population was 1:1 between males and females. None of the subjects had previous experience with opium tincture and were unable to distinguish between the active and placebo treatments in terms of taste and smell.

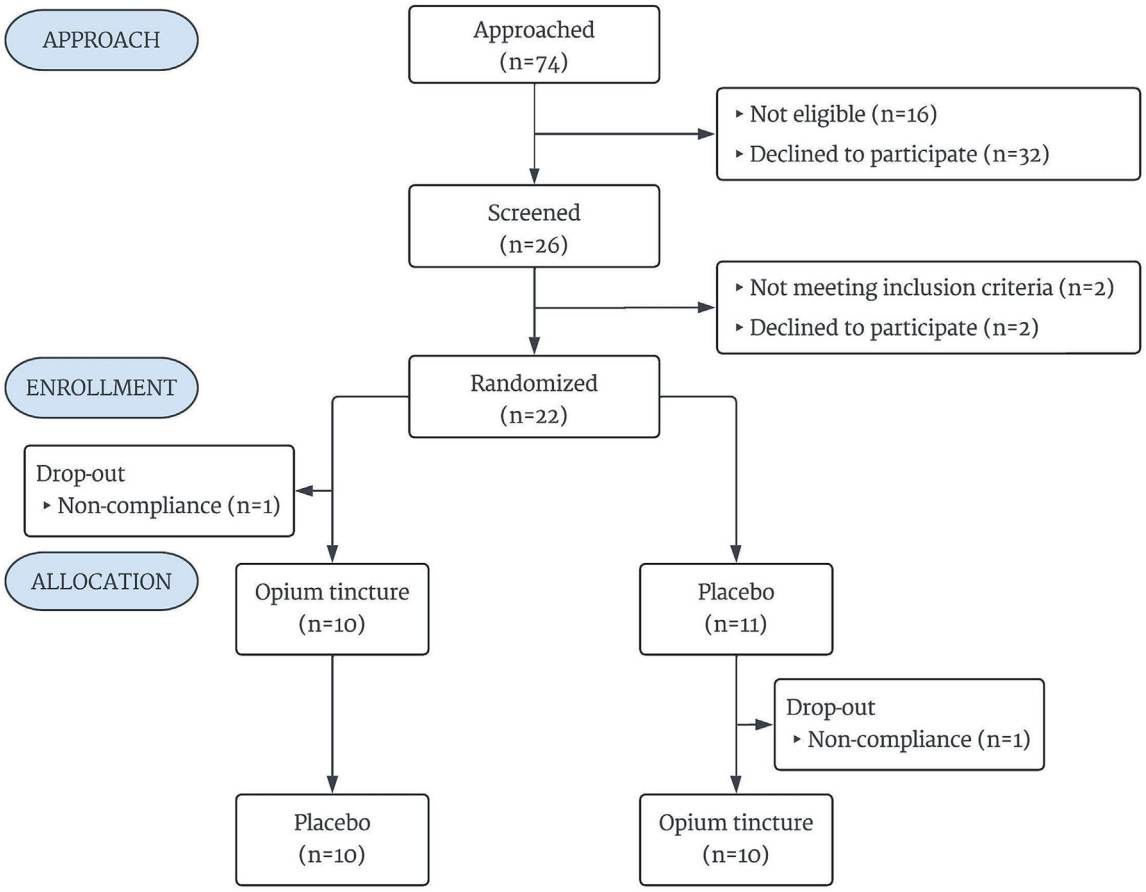

FIGURE 3 Consolidated Standards of Reporting Trials (CONSORT) diagram of the study flow.

3.2 | Effects of opioid tincture on the gastrointestinal tract

3.2.1 | 3D-transit recordings

Technical issues, including sporadic or total loss of signal, led to exclusion of six subjects, which, by chance, were all in the active arm. In addition, a number of various segmental recordings in both arms were unable to be estimated due to high amount of noise in the recording. An overview of viable recordings in each gastrointestinal segment can be found in Table S1.

3.2.2 | Gastrointestinal transit

In 69% (23 of 34) of viable 3D recordings, the diary entry of bowel movement and the time of loss of signal of the capsule coincided. The last data point in the descending colon/sigmoid was used for calculation of whole gut

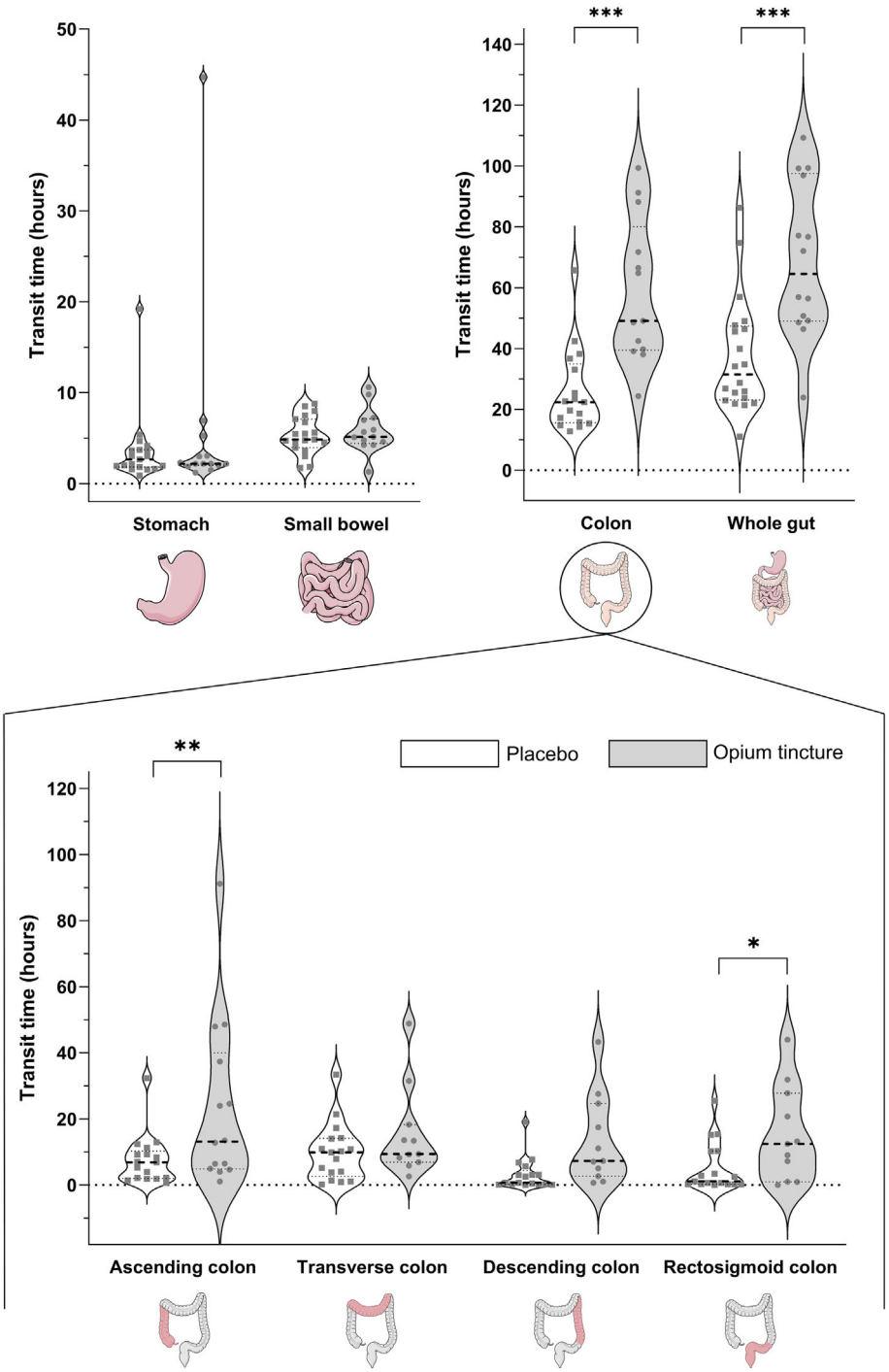

FIGURE 4 Gastrointestinal transit times presented as "violin plots" with individual data points. Unadjusted *p*-value for the overall model is shown above "Whole gut." $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

transit time in 22% of recordings (8 of 34). In the remaining 9% of recordings (3 of 34), the diary-recorded time of next bowel movement was used.

Opium tincture induced no change in gastric emptying time or small bowel transit ($p > 0.05$) (Figure 4). However, colonic transit was more than doubled during active treatment (49 h [40–67] vs. 23 h [16–38], $p < 0.001$). Detailed segmental analysis of the colonic transit revealed that the difference was caused by increased transit in the ascending (13 h [5–37] vs. 7 h [2–9], $p = 0.001$) and rectosigmoid colon (13 h [7–28] vs. 1 h [0.5–10], $p = 0.029$).

3.2.3 | Gastrointestinal motility

Analysis of colonic 3D recordings revealed that the total number of fast and slow antegrade movements and slow retrograde movements was increased during treatment with opium tincture ($p < 0.01$) (Table 1). Contrary to this, the number of long, fast antegrade movements per hour was decreased during active treatment ($p = 0.005$). When looking at the different colonic segments, no differences were seen for either movement type in the ascending or descending colon. Total number of slow antegrade movements was increased in the transverse colon during treatment with opium tincture compared to placebo ($p = 0.013$). In the rectosigmoid colon, total number of both fast ($p = 0.008$) and slow ($p = 0.013$) antegrade movements and slow retrograde movements ($p < 0.001$) was increased during active treatment.

3.2.4 | Spontaneous bowel movements and stool form

Stool type according to Bristol Stool Form Scale was different between placebo and opium tincture treatment (Type 3 [2.8–3.6] vs. Type 4 [3.5–4.4], $p < 0.001$). The post hoc analysis showed that the mean stool consistency was harder at Days 4, 5 and 8 of opium tincture treatment compared to placebo ($p \leq 0.05$) (Figure 5A). Overall mean daily bowel movements during study periods were reduced in all subjects during opium tincture treatment compared to placebo treatment (opium tincture: 0.7 ± 0.4, placebo: 1.2 ± 0.5, $p < 0.001$) (Figure 5B).

3.2.5 | Gastrointestinal symptoms

Global GSRS scores were increased during opium tincture treatment on Days 4 and 6–9 ($p < 0.01$) (Figure 6A6). Symptoms of reflux, abdominal pain and indigestion were also increased on different days during

TABLE 1 Segmental colonic motility patterns during treatment with opium tincture ($n = 13$) or placebo ($n = 17$). Data are presented as median (interquartile range). Unadjusted overall p-value is shown under "Total colon," while segmental p-values are Bonferroni corrected.

		Ascending (#)	Transverse (#)	Descending (#)	Rectosigmoid (#)	Total colon (#)	Total colon (#/hour)
Long, fast antegrade movement	Opium tincture	0 (0–1)	0 (0–1)	0 (0–0)	1 (1–1)	2 (1–3)	0.04 (0.01–0.05)**
	Placebo	0 (0–1)	0 (0–1)	1 (0–1)	1 (1–1)	3 (2–4)	0.13 (0.06–0.19)
Fast antegrade movement	Opium tincture	1 (0–2)	2 (0–6)	1 (0–1)	2.5 (1–8)**	8 (4–16)**	0.12 (0.09–0.22)
	Placebo	1 (1–2)	2 (1–2)	1 (0–2)	2 (1–2)	6 (3–9)	0.24 (0.12–0.51)
Slow antegrade movement	Opium tincture	2 (2–5)	5 (2–10)***	2 (1–4)	2 (2–6)*	13 (7–19)***	0.28 (0.18–0.41)
	Placebo	3 (1–3)	1 (1–2)	1 (0–2)	1 (0–1)	6 (5–7)	0.26 (0.21–0.36)
Slow retrograde movement	Opium tincture	1 (0–1)	1 (0–4)	0 (0–0)	3 (0–8)***	8 (1–11)***	0.11 (0.03–0.23)
	Placebo	0 (0–0)	0 (0–2)	0 (0–1)	0 (0–1)	2 (1–3)	0.08 (0.02–0.15)

*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

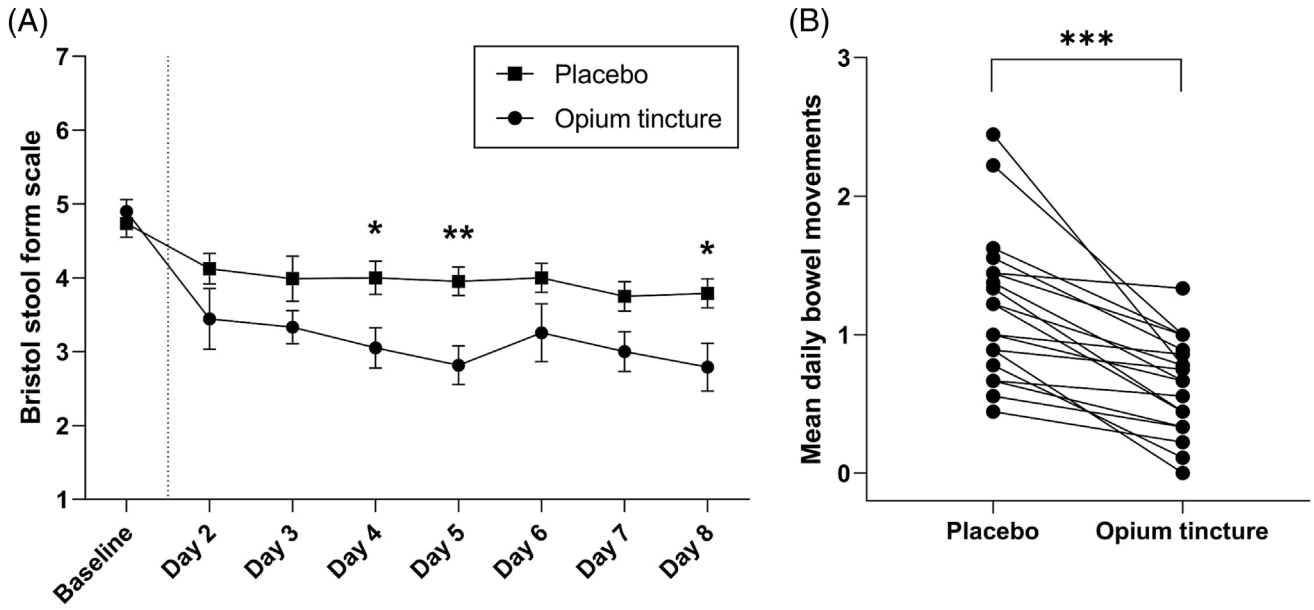

FIGURE 5 (A) Stool type measured on the Bristol Stool Form Scale. Data displayed as mean ± standard error of the mean. (B) Mean daily bowel movements during placebo or opium tincture treatment. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

opium tincture treatment (Figure 6A1–A3). Symptoms of constipation increased during active treatment on Days 4 and 6–9, with the largest difference seen on Day 7 (opium tincture: 1.3 ± 1.2 vs. placebo: 0.3 ± 0.5, $p < 0.001$) (Figure 6A5). Only symptoms of constipation exceeded the threshold for minor discomfort. No differences in symptoms of diarrhoea between treatments were seen ($p > 0.05$) (Figure 6A4). Global PAC-SYM score increased at Days 6–9 ($p < 0.01$), abdominal-related symptoms were increased on Day 6 ($p < 0.05$) (Figure 6B1), while rectal-related symptoms were increased on Days 7 and 8 ($p < 0.01$) during opium tincture treatment (Figure 6B2). Stool-related symptoms were increased during active treatment at Days 6–9 ($p < 0.05$) (Figure 6B3,B4). The symptoms were, however, rated very mild (below 1 on the Likert scale).

3.3 | Effects of opioid tincture on the central nervous system

No differences in Mini-Mental State Examination scores or the digit span test were seen between treatments ($p > 0.05$). Likewise, reaction times were independent of treatment ($p > 0.05$), though a slight tendency towards better performances on Days 6 and 9 compared to baseline was observed during both treatment periods. Mean pupil size decreased during opium tincture treatment compared to placebo confirming that the active drug was taken (Day 6: 4.7 mm ± 1.0 vs. 5.5 mm ± 1.3, $p < 0.01$; Day 9: 4.6 mm ± 0.9 vs. 5.3 mm ± 1.3, $p < 0.01$) (Table 2).

3.3.1 | EEG

Overall theta-band activity was increased, and overall beta band was decreased ($p < 0.001$) during opium tincture treatment compared to placebo. In both bands, post hoc analysis revealed that the difference was found in the frontal ($p < 0.05$), the right temporal ($p < 0.01$) and the occipital region ($p < 0.01$) (Figure S1). In the alpha band (where a slowing could indicate drowsiness), an overall difference across brain areas was found ($p < 0.01$), but after post hoc analysis and Bonferroni correction, the difference was nonsignificant. No differences were seen in the delta band.

4 | DISCUSSION

This randomized, double-blinded, placebo-controlled study is the first to confirm that opium tincture slows gastrointestinal transit without causing sedation. It is thereby the first data to provide evidence-based insights to the mechanistic actions of this medication currently marketed as an anti-propulsive agent for treatment of chronic diarrhoea refractory to first-line therapy.

4.1 | Effects of opioid tincture on the gastrointestinal tract

Opium tincture induced no changes in gastric emptying time or small bowel transit but doubled the colonic

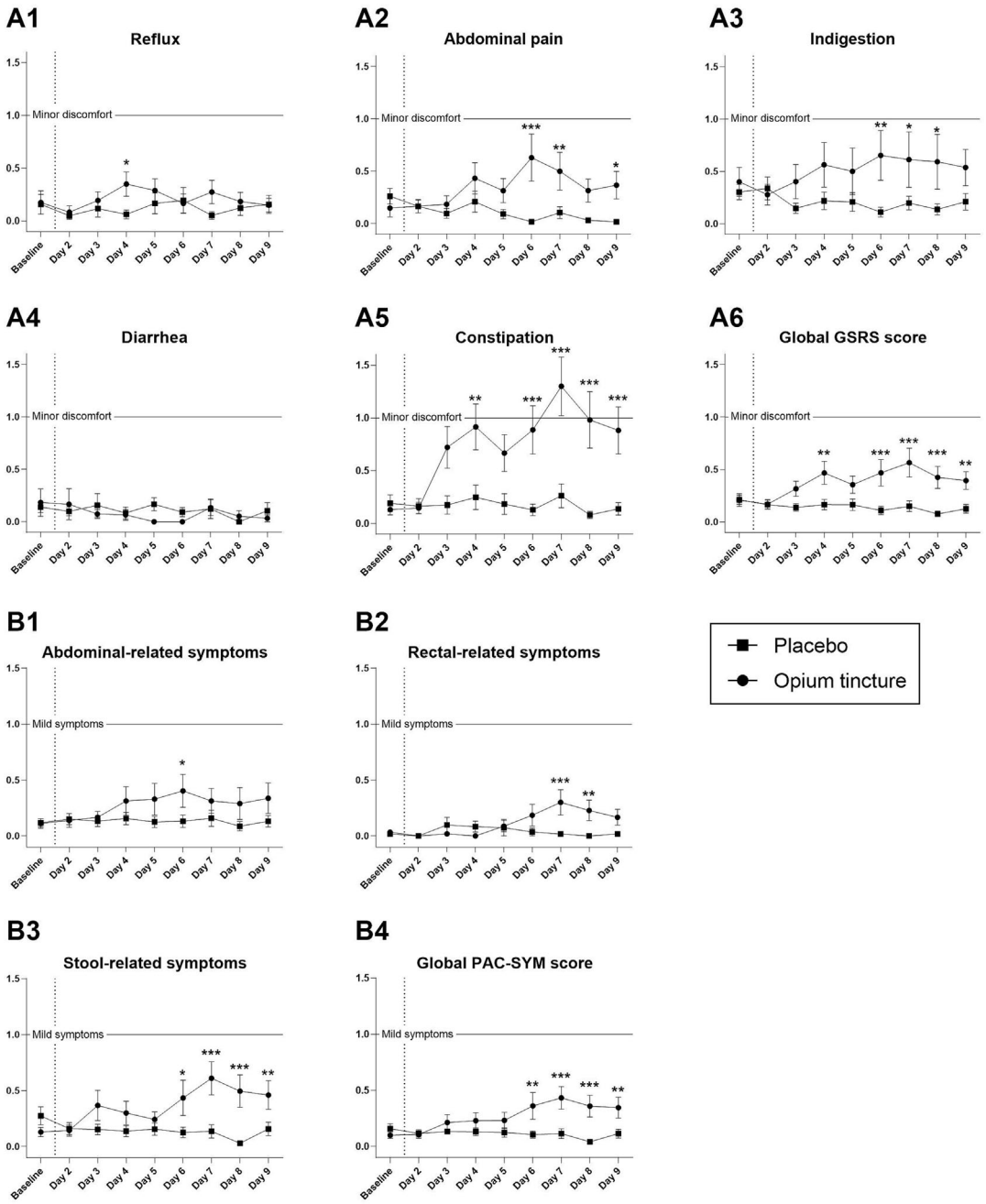

FIGURE 6 Gastrointestinal symptoms measured by (A) Gastrointestinal Symptom Rating Scale (GSRS) and (B) Patient Assessment of Constipation Symptoms (PAC-SYM). Data displayed as mean ± standard error of the mean. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

transit time. This was mainly caused by prolonging the passage through the ascending and rectosigmoid colon. Different opioid responses in the proximal and distal colon regarding transit time and faecal volume have previously been shown in both preclinical and clinical studies.[23–28] The prolonged colonic and whole gut transit times during opium tincture were reflected in bowel movement characteristics. Hence, stool consistency was significantly increased, and all 20 subjects in the study had a reduced number of daily bowel movements during active treatment compared to placebo. These effects of opium tincture were expected based on the well-established inhibitory actions of opioids on gastrointestinal motility and secretion. Similar results with other opioids have previously been reported by our group.[29] Likewise, codeine has been shown to increase gastrointestinal transit,[5,30,31] and studies in experimental diarrhoea have demonstrated how reduced stool volume following opioid treatment is a result of changes in motility and transit times allowing more time for fluid

TABLE 2 Effects of opium tincture on the central nervous system.

		Opium tincture ($n = 20$)	Placebo ($n = 20$)	p-Value
MMSE score (median [min-max])	Baseline	29.5 (24–30)	29 (25–30)	1.000
	Day 6	30 (27–30)	30 (28–30)	0.114
	Day 9	30 (28–30)	30 (29–30)	1.000
CRT 10th percentile (ms) (mean ± SD)	Baseline	159.7 ± 36.3	152.1 ± 16.4	0.323
	Day 6	157.8 ± 33.6	149.7 ± 16.9	0.204
	Day 9	157.4 ± 37.4	153.2 ± 18.2	1.000
CRT 50th percentile (ms) (mean ± SD)	Baseline	188.5 ± 40.7	185.2 ± 26.1	1.000
	Day 6	184.1 ± 38.0	176.8 ± 22.0	0.367
	Day 9	184.9 ± 41.5	179.4 ± 23.1	0.846
CRT 90th percentile (ms) (mean ± SD)	Baseline	238.1 ± 47.9	234.6 ± 35.1	1.000
	Day 6	231.1 ± 43.6	223.8 ± 37.8	0.598
	Day 9	231.4 ± 53.6	225.4 ± 40.1	1.000
CRT index (mean ± SD)	Baseline	2.5 ± 0.6	2.4 ± 0.5	1.000
	Day 6	2.6 ± 0.7	2.6 ± 0.6	1.000
	Day 9	2.6 ± 0.6	2.7 ± 0.7	1.000
DST forward (#) (mean ± SD)	Baseline	5.5 ± 1.9	5.7 ± 1.1	1.000
	Day 6	5.5 ± 1.2	6.1 ± 0.9	0.166
	Day 9	6.0 ± 1.5	5.6 ± 1.4	0.737
DST backward (#) (mean ± SD)	Baseline	4.8 ± 1.0	5.5 ± 2.0	0.135
	Day 6	5.6 ± 1.6	5.1 ± 2.2	0.703
	Day 9	5.1 ± 1.8	5.7 ± 1.8	0.431
Pupil size (mm) (mean ± SD)	Baseline	5.5 ± 1.0	5.6 ± 1.4	1.000
	Day 6	4.7 ± 1.0	5.5 ± 1.3	**0.001**
	Day 9	4.6 ± 0.9	5.3 ± 1.3	**0.006**

Note: Bold font indicates statistical significance ($p < 0.05$).

Abbreviations: CRT, continuous reaction time; DST, digit span test; MMSE, Mini-Mental State Examination.

absorption rather than an increased fluid absorption rate of the intestinal mucosal cells per se.[32,33] The direct underlying mechanism behind these effects, that is, activation of μ-opioid receptors within the submucosal and myenteric plexus of the enteric nervous system, is evident by the alleviation of constipation symptoms during opioid treatment when a peripherally acting μ-opioid receptor antagonist is co-subscribed.[25,34–36] The current study confirms for the first time that opium tincture possesses gastrointestinal-altering actions in healthy, which could also be beneficial in the treatment of chronic diarrhoea.

Previous studies regarding segmental transit time in chronic diarrhoea patients treated with opioids are very limited, but two randomized controlled trials have shown that loperamide decreased gastric emptying time.[37,38] Opioid therapy is usually associated with increased pyloric muscle tone, and the decreased gastric emptying time in these studies is thus contradictory.[39] In both studies, however, the net effect of loperamide treatment was an increase in whole gut transit time, thus achieving the desired anti-propulsive effect for this patient group. In our study, we observed no differences in gastric emptying time between opium tincture and placebo. Seemingly, this discrepancy indicates that opium tincture and loperamide have different mechanistic effects on the enteric nervous system of the stomach, and it could be speculated if this could lead to increased upper gastrointestinal discomfort during loperamide treatment compared to opium tincture. In general, it is largely unknown what underlies the segmental differences in opioid response throughout the alimentary tract. A possible explanation could be the variance in the distribution of subclasses of the opioid receptor in different segments and the individual affinity for these subclasses of various exogenous opioid formulations. Opium tincture contains a mixture of

natural exogenous opioids extracted from the opium poppy and may thus display various affinities contrary to, for example, loperamide, only consisting of a single chemically manufactured exogenous opioid.

Opium tincture increased the number of both fast and slow antegrade movements as well as slow retrograde movements in the rectosigmoid colon. Increased antegrade movements seem to contradict the substantially increased transit time in the distal colon but can be explained simply by the prolonged colonic transit time during active treatment. This is evident by the decreased number of long, fast antegrade movements per hour, during active treatment. Furthermore, opioids are known to induce dysmotility causing a non-propulsive movement pattern in which colonic content is moving both back and forth.[40] In this study, the net effect of antegrade and retrograde movements in the rectosigmoid colon clearly was a decreased propulsive motion. Similar findings have been found in previous studies on the effects of opioids on the healthy gut.[12,24] However, decreased number of long, fast antegrade movements has also been reported when comparing oxycodone to placebo.[24] The same decrease was, however, not seen for tapentadol.[24] This underlines the fact that different opioids affect colonic motility in various way. Taken together, the findings of both slow velocities of peristalsis, increased retrograde movements and increased time in the rectosigmoid colon are all factors associated with segmentation, increased fluid uptake and ultimately constipation.[24]

The objective findings of constipation were in line with the findings from the subjective measures. We applied two relevant and validated questionnaires to investigate the subjective experience of gastrointestinal function during opium tincture treatment. While on opioid therapy, 16 of the 20 subjects experienced symptoms of constipation, and of these, three rated the severity to be moderate to severe. For the remaining 13 subjects with symptoms of constipation, symptoms were rated to be of minor to moderate severity. It is noteworthy that although all subjects experienced fewer daily bowel movements during active treatment compared to placebo, four subjects reported no symptoms of constipation thereby underlining the fact that the subjective perception of constipation is diverse among individuals.[41] In addition to constipation-related symptoms, the patient-reported outcomes also revealed increased symptoms of indigestion, abdominal pain and reflux on varying days during opium tincture treatment. Gastrointestinal effects beyond constipation were suspected due to the well-known and diverse effects of opioids on the enteric nervous system.[39] Mean scores, however, did not exceed minor severity in either subdomain.

4.2 | Effects of opioid tincture on the central nervous system

Opioid therapy is known to induce sedation especially during initiation and escalation of dosage, and thus, the ability to operate motor vehicles during treatment may be impaired and is not recommended.[42] However, this concept has been established based on opioid use for analgesic purposes. It is therefore valid to investigate the specific sedative effect of opium tincture in the doses recommended for treating chronic diarrhoea, which, in morphine equivalent doses, are low compared to those typically prescribed for chronic pain patients.

The Mini-Mental State Examination is a crude measure of general cognition normally applied as a screening tool for signs of dementia. As expected, the subjects in this study, which were all well-functioning individuals, scored within the normal range both before and during opium tincture treatment. Perhaps more interestingly, no decline in reaction time or working memory was evident in either of the two study periods. The continuous reaction time test has previously been shown to be able to discriminate between healthy and patients with various conditions known to affect cognition.[18,43] Our results indicate that though opium tincture penetrates the central nervous system, evident by the significant reduction in pupil diameter,[21] neurophysiological performance remains unaffected. However, fatigue, as an adverse reaction, was reported by 40% of subjects during opium tincture treatment compared to 10% during placebo. This subjective perception of fatigue was not clearly reflected in the EEG measurements. Increased power in the alpha band has previously been linked to fatigue and drowsiness[44] and even suggested as a valid indicator for specific mental fatigue during car driving.[45] In this study, though, no differences in the alpha band were observed during opium tincture treatment compared to placebo. Contrary, power differences in the theta and beta band were measurable. This further supports the conclusion that opium tincture does cross the blood-brain barrier and affects the central nervous system. Theta-band activity may also be influenced by fatigue,[44] but our results regarding general cognition and alertness during treatment with opium tincture indicate that the effects on these parameters are limited.

Based on our findings, it is valid to raise the question if the sedative potential of opioids also applies for opium tincture in the dosages used for chronic diarrhoea, which are, as mentioned, typically substantially lower compared to doses applied in chronic pain management. Moreover, tolerance to central effects of opioids often develops during steady treatment.[46] Contrary to this, preclinical experiments and experimental studies on humans suggest

a lack of tolerance to gastrointestinal effects of opioids adding to the clinical finding that the effect, even for low dosages, continues to be effective on diarrhoea without cognitive side effects.[24,26] Accordingly, the issue should be addressed further to ensure that patients in need of opioid therapy for treatment of chronic diarrhoea are not prohibited from operating motor vehicles based on assumptions. This ban may further stigmatize this patient group and hinder a normal everyday life. It is therefore crucial that such measures are only applied, when sufficient evidence is present. Thus, we advocate the need for clinical studies with the primary aim of investigating driving performance and mental fatigue during antidiarrhoeal opioid therapy.

4.3 | Strengths and limitations

The measurement of segmental transit time and motility was assessed by the 3D-transit system available only for research purposes. This system has some advantages compared to established methods such as scintigraphy or radiopaque markers.[47] First, the real-time tracking of the 3D-transit capsule allows for a very detailed recording of motility patterns including both forward and retrograde movements not available through any other transit measurement. Second, the recording is made in an outpatient setting during normal daily routine of subjects, and results may thus reflect normal transit times better than results obtained in hospital settings. Another commercially available motility capsule, the wireless motility capsule, also records the segmental passage of a wireless capsule during normal routine, but the information regarding the specific position of the capsule at any given timepoint is not available.[48] In the present study, we wanted to explore the detailed mechanistic effects of opium tincture on the gastrointestinal tract, and thus, the 3D transit system was chosen. Obvious disadvantages of the 3D-transit system include the risk of failed recordings due to technical issues. In this study, 6 out of 20 recordings in the active arm were excluded for this reason, underlining that the 3D-transit system remains a device not yet developed finally for clinical use. Moreover, it should be noted that the passage of a single solid capsule might provide different mechanistic feedback to the gastrointestinal tract than a bolus of food, likely resulting in different responses in terms of motility patterns. The passing of the 3D-transit capsule has, however, been shown to correlate well with that of radiopaque markers, which are considered a robust investigational approach for gastrointestinal transit time.[49]

In this study, we used a daily dose of opium tincture (Dropizol®) corresponding to the recommended dose for chronic diarrhoea. It is, however, important to note that other opium tincture products exist and that these may have a different recommended dose in terms of morphine equivalence. Consequently, caution should be taken when translating the results presented in this study regarding gastrointestinal function and sedation to other products containing opium tincture. Moreover, raw opium is a complex compound containing multiple opiates, which complicates calculation of morphine equivalence.

The treatment period of 9 days in the current study was relatively short, and the long-term anti-propulsive effects of opium tincture are thus unknown. However, while tolerance of some undesired effects of opioid therapy such as nausea and fatigue often is achieved during stable treatment, opioid-induced constipation is persistent. While this poses a problem when applying opioids for chronic pain management, it is an advantage in the context of treatment of chronic diarrhoea.[2] It would therefore be expected that the anti-propulsive effects of opium tincture on the healthy gastrointestinal tract shown in this study would extend beyond the 9 days of investigation.

A decision to include both males and females in the study was made to enhance the generalizability of the results. However, information regarding menstrual cycle, which is known to affect gastrointestinal function,[50] was not included but could have influenced the results of the female subjects.

4.4 | Conclusion

In conclusion, our results showed that opium tincture induced symptoms of constipation in a cohort of healthy subjects evident by increased colonic transit times, decreased antegrade colonic movements, reduced number of daily bowel movements and increased consistency of stools. No decline in general cognition, reaction time or working memory during opium tincture treatment was observed indicating that opium tincture is safe. Based on these results, opium tincture may represent an evidence-based alternative for chronic diarrhoea patients, where standard therapy such as loperamide has failed.

ACKNOWLEDGEMENTS

This study was funded by an unrestricted grant from Pharmanovia.

CONFLICT OF INTEREST STATEMENT

This investigator-initiated study was funded by an unrestricted grant from Pharmanovia. Pharmanovia did not influence the design or reporting of the study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Tina Okdahl https://orcid.org/0000-0003-2659-4313
Cecilie Siggaard Knoph https://orcid.org/0000-0002-8373-1487
Mathias Ellgaard Cook https://orcid.org/0000-0002-4157-1091

REFERENCES

1. Farmer AD, Drewes AM, Chiarioni G, et al. Pathophysiology and management of opioid-induced constipation: European expert consensus statement. *UEG J*. 2019;7(1):7-20.
2. Coyne KS, Margolis MK, Yeomans K, et al. Opioid-induced constipation among patients with chronic noncancer pain in the United States, Canada, Germany, and the United Kingdom: laxative use, response, and symptom burden over time. *Pain Med*. 2015;16(8):1551-1565.
3. Crockett SD, Greer KB, Heidelbaugh JJ, et al. American Gastroenterological Association Institute guideline on the medical management of opioid-induced constipation. *Gastroenterology*. 2019;156(1):218-226.
4. Wood JD, Galligan JJ. Function of opioids in the enteric nervous system. *Neurogastroenterol Motil*. 2004;16(SUPPL. 2):17-28.
5. Barrow L, Steed KP, Spiller RC, et al. Quantitative, noninvasive assessment of antidiarrheal actions of codeine using an experimental model of diarrhea in man. *Dig Dis Sci*. 1993;38(6):996-1003.
6. Hoyle CH, Kamm MA, Burnstock G, et al. Enkephalins modulate inhibitory neuromuscular transmission in circular muscle of human colon via delta-opioid receptors. *J Physiol*. 1990;431(1):465-478.
7. Schiller LR, Pardi DS, Sellin JH. Chronic diarrhea: diagnosis and management. *Clin Gastroenterol Hepatol*. 2017;15(2):182-193.e3.
8. Heydari M, Hashempur MH, Zargaran A. Medicinal aspects of opium as described in Avicenna's Canon of Medicine. *Acta Med Hist Adriat*. 2013;11(1):101-112.
9. White WL. Selected papers of William L. White—opium in America: the early story [Internet]. Accessed October 13, 2022. www.williamwhitepapers.com
10. Tveden-Nyborg P, Bergmann TK, Jessen N, et al. BCPT policy for experimental and clinical studies. *Basic Clin Pharmacol Toxicol*. 2021;128(1):4-8.
11. Haase AM, Gregersen T, Schlageter V, et al. Pilot study trialling a new ambulatory method for the clinical assessment of regional gastrointestinal transit using multiple electromagnetic capsules. *Neurogastroenterol Motil*. 2014;26(12):1783-1791.
12. Mark EB, Poulsen JL, Haase AM, et al. Ambulatory assessment of colonic motility using the electromagnetic capsule tracking system. *Neurogastroenterol Motil*. 2019;31(2):e13451. doi:10.1111/nmo.13451
13. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol*. 1997;32(9):920-924.
14. Svedlund J, Sjödin I, Dotevall G. GSRS—a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Dig Dis Sci*. 1988;33(2):129-134.
15. Yiannakou Y, Tack J, Piessevaux H, et al. The PAC-SYM questionnaire for chronic constipation: defining the minimal important difference. *Aliment Pharmacol Ther*. 2017;46(11–12):1103.
16. Crum RM, Anthony JC, Bassett SS, et al. Population-based norms for the Mini-Mental State Examination by age and educational level. *JAMA J Am Med Assoc*. 1993;269(18):2386-2391.
17. Jakobsen LH, Sorensen JM, Rask IK, et al. Validation of reaction time as a measure of cognitive function and quality of life in healthy subjects and patients. *Nutrition*. 2011;27(5):561-570.
18. Elsass P. Continuous reaction times in cerebral dysfunction. *Acta Neurol Scand*. 1986;73(3):225-246.
19. Diasso PDK, Sjøgren P, Højsted J, et al. Patient reported outcomes and neuropsychological testing in patients with chronic non-cancer pain in long-term opioid therapy: a pilot study. *Scand J Pain*. 2019;19(3):533-543.
20. Matuoka JY, Kurita GP, Nordly M, et al. Validation of a battery of neuropsychological tests for patients with metastatic cancer. *Clin Nurs Res*. 2020;29(8):607-615.
21. Fischer IW, Hansen TM, Lelic D, et al. Objective methods for the assessment of the spinal and supraspinal effects of opioids. *Scand J Pain*. 2017;(14):15-24.
22. Pion-Tonachini L, Kreutz-Delgado K, Makeig S. ICLabel: an automated electroencephalographic independent component classifier, dataset, and website. *Neuroimage*. 2019;(198):181-197.
23. Ono H, Nakamura A, Matsumoto K, et al. Circular muscle contraction in the mice rectum plays a key role in morphine-induced constipation. *Neurogastroenterol Motil*. 2014;26(10):1396-1407.
24. Mark EB, Nedergaard RB, Hansen TM, et al. Tapentadol results in less deterioration of gastrointestinal function and symptoms than standard opioid therapy in healthy male volunteers. *Neurogastroenterol Motil*. 2021;33(11):e14131. doi:10.1111/nmo.14131
25. Olesen AE, Gronlund D, Mark EB, et al. Effects of naloxegol on gastrointestinal transit and colonic fecal volume in healthy participants receiving oxycodone. *J Neurogastroenterol Motil*. 2019;25(4):602-610.
26. Poulsen JL, Mark EB, Brock C, et al. Colorectal transit and volume during treatment with prolonged-release oxycodone/naloxone versus oxycodone plus macrogol 3350. *J Neurogastroenterol Motil*. 2018;24(1):119-127.
27. Nilsson M, Poulsen JL, Brock C, et al. Opioid-induced bowel dysfunction in healthy volunteers assessed with questionnaires and MRI. *Eur J Gastroenterol Hepatol*. 2016;28(5):514-524.
28. Poulsen JL, Nilsson M, Brock C, et al. The impact of opioid treatment on regional gastrointestinal tTransit. *J Neurogastroenterol Motil*. 2016;22(2):282-291.
29. Mark EB, Frøkjær JB, Hansen TM, et al. Although tapentadol and oxycodone both increase colonic volume, tapentadol

treatment resulted in softer stools and less constipation: a mechanistic study in healthy volunteers. *Scand J Pain*. 2021;21(2):406-414.
30. Gonenne J, Camilleri M, Ferber I, et al. Effect of alvimopan and codeine on gastrointestinal transit: a randomized controlled study. *Clin Gastroenterol Hepatol*. 2005;3(8):784-791.
31. Wong BS, Rao AS, Camilleri M, et al. The effects of methylnaltrexone alone and in combination with acutely administered codeine on gastrointestinal and colonic transit in health. *Aliment Pharmacol Ther*. 2010;32(7):884-893.
32. Schiller LR, Davis GR, Santa Ana CA, et al. Studies of the mechanism of the antidiarrheal effect of codeine. *J Clin Invest*. 1982;70(5):999-1008.
33. Schiller LR, Santa Ana CA, Morawski SG, et al. Mechanism of the antidiarrheal effect of loperamide. *Gastroenterology*. 1984;86(6):1475-1480.
34. Ouyang R, Li Z, Huang S, et al. Efficacy and safety of peripherally acting mu-opioid receptor antagonists for the treatment of opioid-induced constipation: a Bayesian network meta-analysis. *Pain Med*. 2020;21(11):3224-3232.
35. Grønlund D, Poulsen JL, Krogh K, 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;30(117):187-192.
36. Poulsen JL, Brock C, Grønlund D, et al. Prolonged-release oxycodone/naloxone improves anal sphincter relaxation compared to oxycodone plus macrogol 3350. *Dig Dis Sci*. 2017;62(11):3156-3166.
37. Cann PA, Read NW, Holdsworth CD, et al. Role of loperamide and placebo in management of irritable bowel syndrome (IBS). *Dig Dis Sci*. 1984;29(3):239-247.
38. Yeoh EK, Horowitz M, Russo A, et al. Gastrointestinal function in chronic radiation enteritis—effects of loperamide-N-oxide. *Gut*. 1993;34(4):476-482.
39. Holzer P. Opioid receptors in the gastrointestinal tract. *Regul Pept*. 2009;155(1–3):11-17.
40. Poulsen JL, Brock C, Olesen AE, et al. Clinical potential of naloxegol in the management of opioid-induced bowel dysfunction. *Clin Exp Gastroenterol*. 2014;19(7):345-358.
41. Grønlund D, Vase L, Knudsen SA, et al. Comparison of subjective and objective measures of constipation—employing a new method for categorizing gastrointestinal symptoms. *J Pharmacol Toxicol Methods*. 2018;94(Pt 2):23-28.
42. Reissig JE, Rybarczyk AM. Pharmacologic treatment of opioid-induced sedation in chronic pain. *Ann Pharmacother*. 2005;39(4):727-731.
43. Lauridsen MM, Grønbæk H, Næser EB, et al. Gender and age effects on the continuous reaction times method in volunteers and patients with cirrhosis. *Metab Brain Dis*. 2012;27(4):559-565.
44. Craig A, Tran Y, Wijesuriya N, et al. Regional brain wave activity changes associated with fatigue. *Psychophysiology*. 2012;49(4):574-582.
45. Gharagozlou F, Saraji GN, Mazloumi A, et al. Detecting driver mental fatigue based on EEG alpha power changes during simulated driving. *Iran J Public Health*. 2015;44(12):1693.
46. Sjøgren P, Olsen AK, Thomsen AB, et al. Neuropsychological performance in cancer patients: the role of oral opioids, pain and performance status. *Pain*. 2000;86(3):237-245.
47. Lin HC, Prather C, Fisher RS, et al. Measurement of gastrointestinal transit. *Dig Dis Sci*. 2005;50(6):989-1004.
48. Farmer AD, Scott SM, Hobson AR. Gastrointestinal motility revisited: the wireless motility capsule. *United Eur Gastroenterol J*. 2013;1(6):413-421.
49. Camilleri M, Thorne NK, Ringel Y, et al. Wireless pH-motility capsule for colonic transit: prospective comparison with radiopaque markers in chronic constipation. *Neurogastroenterol Motil*. 2010;22(8):874-e233. doi:10.1111/j.1365-2982.2010.01517.x
50. Judkins TC, Dennis-Wall JC, Sims SM, et al. Stool frequency and form and gastrointestinal symptoms differ by day of the menstrual cycle in healthy adult women taking oral contraceptives: a prospective observational study. *BMC Womens Health*. 2020;20(1):136. doi:10.1186/s12905-020-01000-x

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Okdahl T, Mark EB, Nedergaard RB, et al. Effects of opium tincture on the enteric and central nervous systems: A randomized controlled trial. *Basic Clin Pharmacol Toxicol*. 2023;132(5):434-448. doi:10.1111/bcpt.13850