

# Effects of pain on cognitive function and mobility

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**Background:** Chronic pain has been associated with impaired cognitive function as well as limitations in physical mobility in older adults. This study was conducted to determine whether acute pain that is typically self-diagnosed and self-treated with nonprescription analgesics also affects cognitive function or mobility.

**Methods:** In this placebo-controlled, randomized study, generally healthy adults with recurrent acute joint, back, head, or menstrual pain underwent assessments of cognitive function (Axon Sports Priming Application, Cambridge Neuropsychological Test Automated Battery) and mobility (gait, time to stand, and grip force) during pain ( $\geq 5$  out of 10 on Brief Pain Inventory – Short Form Q6) vs after pain resolution. Assessments during pain were made before and after treatment with paracetamol 500 mg, paracetamol 500 mg/caffeine 65 mg, or placebo. Primary and secondary outcomes, respectively, were the effects of pain on cognition and mobility vs the pain-free state. The effects of nonprescription analgesics on these outcomes were intended as an exploratory outcome but were not analyzed due to early termination of the study for breaches of Good Clinical Practice guidelines.

**Results:** At termination, 54 individuals had been screened and 21 randomized (safety population). The primary analysis population (modified intent-to-treat) consisted of 20 participants with no inclusion/exclusion violations. Due to early termination, the study did not meet prespecified recruitment levels; therefore, no conclusions could be drawn regarding the effects of pain on cognitive performance or mobility. There were three treatment-emergent adverse events (placebo: reflux disease and hypercholesterolemia; paracetamol: pharyngeal erythema).

**Conclusion:** Because the study was terminated before reaching prespecified recruitment levels, conclusions cannot be drawn regarding the effects of pain or relief from pain by analgesics on cognition or mobility. However, the methodology can serve as a model for addressing these important questions in future investigations. Safety results were consistent with the safety profile for nonprescription paracetamol and paracetamol/caffeine.

**Keywords:** pain, cognition, mobility limitation, paracetamol, caffeine

## Introduction

Chronic pain conditions have been associated with impairments in cognitive function, including speed of information processing, reasoning ability, attention, working memory, and long-term memory.<sup>1-7</sup> In addition, studies of community-dwelling older adults found that pain, particularly widespread or severe pain, was associated with mobility limitations.<sup>8-11</sup> Limitations in physical performance (eg, walking speed, stair climbing, and activities of daily living) have been observed in individuals with knee or hip osteoarthritis and correspond to the pain level.<sup>12,13</sup> Finally, both pain and cognitive

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impairment affect mobility status in older adults, and mobility is affected to a greater extent when both are present.<sup>14</sup>

Little is known about whether common types of pain that are often self-treated with nonprescription therapies (eg, joint, back, head, and menstrual pain) have similar effects on cognitive function or mobility in the general adult population. If such cognitive and mobility impairments do occur, it is unknown whether over-the-counter analgesics have the ability to reduce these deficits either via direct effects on the central nervous system (CNS) or indirectly by reducing pain. Paracetamol is known to penetrate the blood–brain barrier into the CNS.<sup>15</sup> Therefore, it is believed to have a central effect on pain that may involve neurotransmitters (eg, serotonin) that are also involved in decision making and other cognitive tasks.<sup>16–18</sup> Data on the effects of paracetamol on cognition and mobility in individuals with pain, however, are lacking. Although one double-blind, randomized, placebo-controlled, repeated-dose clinical study in 72 healthy men with exercise-induced leg muscle pain found no improvement in cognitive or motor skills with ibuprofen,<sup>19</sup> another randomized, placebo-controlled study conducted in 40 healthy volunteers found that a single oral 2 g dose of paracetamol improved cognitive function, particularly decision making and spatial memory;<sup>18</sup> whether lower nonprescription doses have similar effects has not been established. It is also unknown whether the addition of caffeine to paracetamol would enhance any potential benefits regarding cognitive function or mobility, but such effects are plausible because caffeine increases the analgesic effects of paracetamol, may shorten the time to paracetamol onset,<sup>20–22</sup> and has been shown to enhance alertness/vigilance and reaction time among healthy individuals.<sup>23–25</sup>

To address these knowledge gaps, this study was designed to assess the effects of common joint, back, head, or menstrual pain on cognition (primary objective) and mobility (secondary objective) compared with a pain-free state. Exploratory end points were intended to compare the effects of paracetamol and paracetamol/caffeine vs placebo on cognition and mobility in participants with pain. Unfortunately, it was not possible to fully evaluate the primary and secondary end points or calculate the exploratory end points because the study was terminated due to breaches of Good Clinical Practice guidelines observed during the sponsor's internal audit. These breaches pertained to technical aspects of data storage, handling, and transmission, such that data were not all transmitted via the secured systems required by the study protocol. These breaches did not affect participant safety or compromise personally identifiable information, as such

information was not recorded on the case report forms. The methodology of this study may be useful in designing future studies to address these important questions.

## Materials and methods

### Study design and procedures

This parallel, assessor-blind, placebo-controlled, stratified, randomized study was conducted from October 31, 2016 to February 6, 2017 (ClinicalTrials.gov Identifier: NCT02974114; EudraCT: 2015-002330-42). Participants made three visits to the study center (GSK Human Performance Lab, Brentford, Middlesex, UK). Visit 1 was for participant screening and collection of baseline and demographic data. At Visit 2 (7–28 days after Visit 1), assessments of cognition (Axon Sports Priming Application and Cambridge Neuropsychological Test Automated Battery [CANTAB]) and mobility were conducted while the participant was experiencing pain. Pain was confirmed by a score of 5 or greater on the Brief Pain Inventory (BPI) – Short Form (question 6; numerical rating of pain severity from 0= no pain to 10= pain as bad as you can imagine).<sup>26</sup> Cognition and mobility assessments were made both before and after pain treatment at Visit 2. These assessments were repeated at Visit 3 (2–30 days after Visit 2) with the participant in a pain-free state. The absence of pain at Visit 3 was confirmed by score of 0 on the BPI – Short Form.

Cognitive testing consisted of the Axon Sports Priming Application and the CANTAB,<sup>27–29</sup> which were administered via electronic tablet device at Visits 2 and 3. The Axon Sports Priming Application is a mobile version of the simple reaction time task from the CogState computerized cognitive assessment battery;<sup>30</sup> it consists of a 5-minute computerized test that measures psychomotor speed (primarily simple reaction time) in milliseconds. The CANTAB assessments used in this study included tests of reaction time, executive function (via the One Touch Stockings of Cambridge task and the Attention Switching Task), spatial working memory, and rapid visual information processing.<sup>29</sup>

Mobility assessments included evaluations of gait, time to stand, and grip force.<sup>31</sup> Gait assessments included duration of contact with the ground (ie, time from initial heel strike to lifting of toe, in m/s), stride length (cm), and walking speed over 5–10 m for each foot (m/s). At each assessment period, participants completed three walk tests over a 15 m track with only a 5- to 10-m section measured and analyzed; three sit-to-stand tests; and three grip force tests; the results for each set were averaged. The Optojump athletic movement analysis system (Microgate) was used in the analyses of gait.

Time to stand from a seated position was measured with a stopwatch, and ground reaction force was measured with a force plate. Grip force in the dominant hand was assessed using a dynamometer, with the participant exerting the maximum effort possible during arm swinging from above the head to the side of the body. If pain was present in the dominant hand, grip force was measured in the nondominant hand instead.

## Study population and restrictions

Participants were required to be generally healthy men and women, 18–65 years of age, with a body mass index (BMI) of 18.5–30 kg/m<sup>2</sup>, who were experiencing a transient episode of only one of the following: joint, back, head, or menstrual pain. They had to have a minimum of two recurrent, acute pain episodes in the past 3 months or a current flare-up of recurrent, acute pain at Visit 1, and a score of at least 5 (on a 0–10 numerical rating scale) on question 6 of the BPI – Short Form questionnaire in the pretreatment stage of Visit 2. Women of childbearing potential had to be using a reliable method of contraception, and all participants had to be able and willing to comply with study procedures, assessments, and restrictions. Participants were recruited from GlaxoSmithKline employees, the general local population via advertisement, and from a panel of pain sufferers held by the study center.

Exclusion criteria included the presence of any medical condition that might be aggravated by the test procedures or that might impact interpretation of the results (in the opinion of the investigator), color blindness, pregnancy or lactation, use of antidepressants within 2 years prior to the study, hypersensitivity to study interventions or related compounds, and positive breath test results for alcohol or urine test results for drugs of abuse at Visit 2. Individuals with current (within 14 days of study start) or regular use of any prescription, over-the-counter, or herbal medicine were excluded unless the medication was approved by the study physician. Current smokers, heavy drinkers (>21 units/week for men or >14 units/week for women), and those with frequent caffeine intake equivalent to six cups of brewed coffee or 12 cups of tea per day were also excluded. Potential participants were excluded if they had participated in another clinical trial or received an investigational drug within 1 week of the screening visit, or if they were employees or immediate family members of employees at the study center.

Analgesics, anti-inflammatory agents, and vitamin supplements were prohibited within 48 hours of Visits 2 and 3. Medications that might counteract paracetamol and/or

caffeine were prohibited on assessment days, and antidepressants were prohibited for the duration of the study. Consumption of any substance known to induce or inhibit hepatic drug metabolism was prohibited in the 30 days prior to dosing. During the study, participants were required to refrain from excessive consumption of alcohol for 24 hours prior to Visits 2 and 3 and from consuming caffeine for 4 hours prior to these visits. While on site, participants were not permitted to smoke or to consume food, fluids, or medications other than the study medication and water provided.

All participants provided written informed consent at Visit 1, prior to any assessments or interventions. The study was reviewed and approved on August 9, 2016, by the East Midlands – Leicester South Research Ethics Committee, NHS and conducted in accordance with local laws and regulations as well as the Declaration of Helsinki.

## Interventions

At Visit 2, participants were randomly assigned to one of the following three treatment groups: paracetamol 500 mg+ caffeine 65 mg (Panadol<sup>®</sup> Extra Advance; GlaxoSmithKline Consumer Healthcare [GSKCH], Warren, NJ, USA), paracetamol 500 mg (Panadol<sup>®</sup> Advance, GSKCH), or placebo matched to Panadol<sup>®</sup> Extend (GSKCH). All groups received a single oral dose consisting of two tablets taken with 200 mL of water. The three treatments had different appearances; however, participants wore an eye mask during dosing, and study site personnel involved in dispensing and administration were not involved in any of the cognition and mobility assessments. The investigators and statisticians were not present during dosing and were blinded to treatment assignment.

Randomization was stratified by baseline pain type (knee or hip joint pain, upper or lower back pain, headache, or menstrual pain). Assessments of pain, cognition, and mobility were conducted prior to treatment and at 75 minutes posttreatment.

## Study outcomes

The primary outcome was a comparison of cognitive performance based on Axon Sports and CANTAB assessments during pain (Visit 2, pretreatment) vs a pain-free state (Visit 3). The secondary outcome was a comparison of mobility based on gait, time to stand, and ground reaction force during pain (pretreatment) vs the pain-free state. Safety data (adverse events [AEs], serious AEs) were collected throughout the study beginning with Visit 1, and all AEs were evaluated with regard to severity and causality.

## Statistics

According to the study protocol, ~65 participants were to be randomized to ensure that ~60 evaluable participants would complete the study (~20 participants per treatment arm). However, enrollment was not completed because of the early study termination.

The safety population was defined as all participants receiving treatment, and the intent-to-treat (ITT) population was defined as all participants who received treatment and had at least one postbaseline efficacy measurement. The modified ITT (mITT) population, which was the primary analysis population, was defined as participants from the ITT population who had no violations of protocol-defined inclusion/exclusion criteria.

Descriptive statistics were calculated for all efficacy outcomes. A nonparametric Wilcoxon signed-rank test was performed to analyze time-related efficacy end points (Axon Sports assessment, reaction time, attention-switching task, contact phases, walking speed, and time to stand). A two-sided paired *t*-test was performed for end points that were not time-related (Rapid Visual Information Processing, Spatial Working Memory, One Touch Stockings of Cambridge, stride length, ground reaction force, and grip force), and 95% CIs

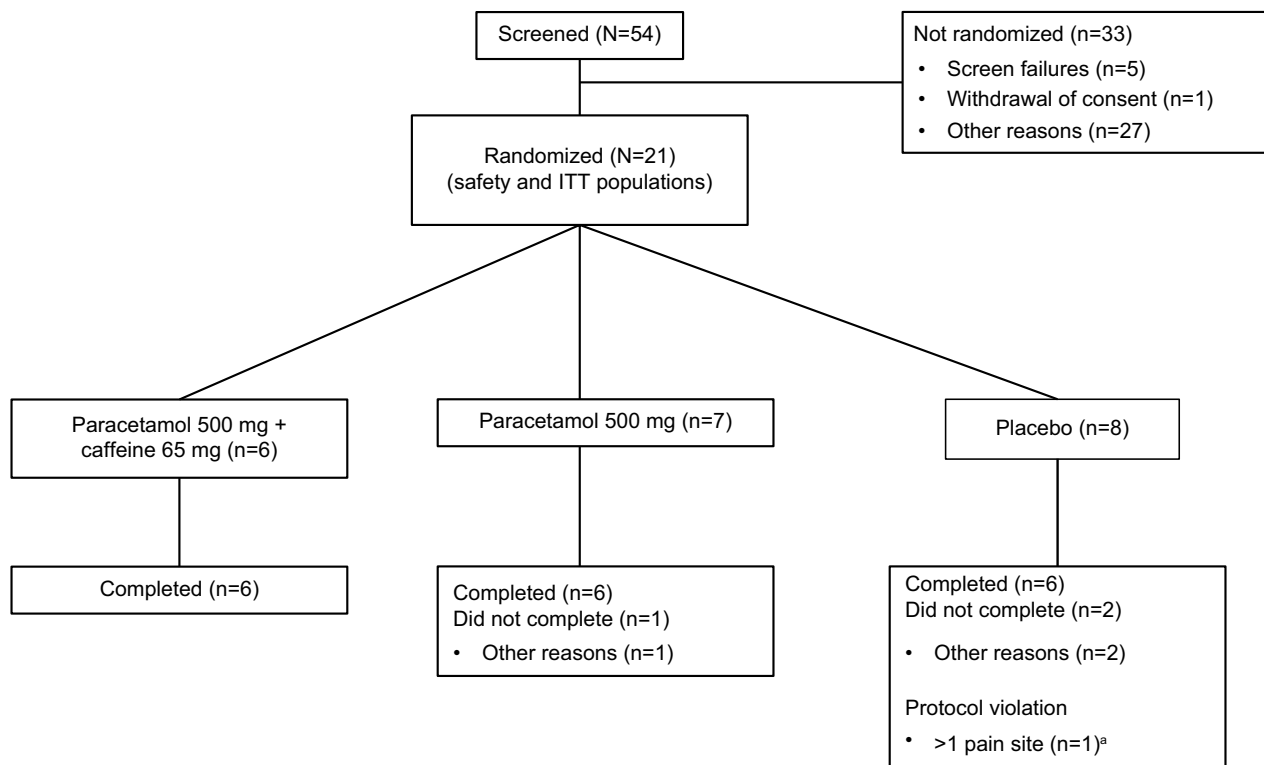
were calculated. For the parametric analyses, assumptions of normality were investigated and, if unconfirmed, an appropriate data transformation or nonparametric method was used. No adjustments were made for multiplicity, and no imputations were made for missing data. All statistical analyses were performed using SAS software version 9.2.

Planned exploratory analyses comparing the effects of the treatment interventions (posttreatment vs pretreatment) on cognition and mobility during the pain state were not conducted due to early study termination. Therefore, only the pretreatment data from Visit 2 are reported and compared with the assessments in the pain-free state at Visit 3.

## Results

### Study population

At the time of the early study termination, 54 individuals had been screened and 21 randomized (Figure 1). The 21 randomized participants comprised both the ITT and safety populations. This group was 66.7% female, 57.1% White, and had a mean age of 33.2 years (Table 1). One of the randomized participants had a protocol violation consisting of having two pain sites (hip and lower back) and was therefore



**Figure 1** Participant disposition.

**Note:** <sup>a</sup>One subject in the placebo group had a protocol violation, completed the study, but was excluded from the mITT population; therefore, total mITT population n=20.  
**Abbreviations:** ITT, intent-to-treat; mITT, modified intent-to-treat.

**Table 1** Demographic characteristics

	Paracetamol 500 mg+ caffeine 65 mg (n=6)	Paracetamol 500 mg (n=7)	Placebo (n=8)	Overall (N=21)
Sex, n (%)				
Female	4 (66.7)	5 (71.4)	5 (62.5)	14 (66.7)
Male	2 (33.3)	2 (28.6)	3 (37.5)	7 (33.3)
Race, n (%)				
White	3 (50.0)	5 (71.4)	4 (50.0)	12 (57.1)
Asian	2 (33.3)	2 (28.6)	1 (12.5)	5 (23.8)
Black	1 (16.7)	0	2 (25.0)	3 (14.3)
Multiple	0	0	1 (12.5)	1 (4.8)
Age, years				
Mean $\pm$ SD	27.8 $\pm$ 4.8	30.0 $\pm$ 9.5	40.0 $\pm$ 15.9	33.2 $\pm$ 12.3
Range	20–35	20–47	26–63	20–63
BMI, kg/m <sup>2</sup>				
Mean $\pm$ SD	22.30 $\pm$ 2.5	23.5 $\pm$ 2.5	24.3 $\pm$ 3.3	23.5 $\pm$ 2.8
Range	18.7–24.5	20.3–27.4	20.1–27.8	18.7–27.8

**Abbreviation:** BMI, body mass index.

excluded from the mITT population. Eighteen participants completed the study.

## Effects of pain on cognition and mobility

There were insufficient data to allow for observation of any trends regarding the effects of pain (pretreatment) on cognitive performance compared with the pain-free state (Table 2). Results in this small population were highly variable with few significant differences. Similarly, no clear trend could be discerned regarding how pain affected mobility (Table 3).

## Safety

There were seven total AEs (Table 4), of which three were treatment-emergent (acid reflux, worsening hypercholesterolemia, and pharyngeal erythema). All were mild to moderate. None were considered treatment-related or serious, and all resolved. None of the participants withdrew from the study as a result of an AE.

## Discussion

Definitive conclusions about the effects of pain on cognition and mobility cannot be drawn from this study due to the high variability of the results and the insufficient sample size resulting from early study termination. Safety results were consistent with the known safety profile for an over-the-counter dose of paracetamol<sup>32</sup> or paracetamol/caffeine.<sup>22,33</sup> One case of mild pharyngeal erythema on the day of paracetamol administration was the only treatment-emergent

AE associated with either active treatment, and it was not considered treatment-related.

The adverse effect of pain on cognitive function has been demonstrated in numerous studies of patients with various chronic pain conditions such as rheumatoid arthritis, fibromyalgia, neuropathic pain, and persistent low back or neck pain.<sup>1–7</sup> These effects may be mediated by depression<sup>1</sup> or may occur because cognitive tasks are competing with pain for attentional resources.<sup>3,34</sup> Another hypothesis is that closely linked neurologic signaling pathways involved in cognition and pain transmissions may modulate each other.<sup>34</sup> In addition, chronic pain may result in altered neuroplasticity or dysregulated neurochemistry that in turn affects cognitive function.<sup>34</sup>

Data are lacking in terms of whether similar mechanisms would also lead to impairments in cognition in pain that would ordinarily be treated with nonprescription analgesics. Similarly, it is unclear whether the mobility limitations observed in older adults with severe or widespread pain<sup>8–10</sup> or osteoarthritis<sup>13</sup> would also occur in younger populations or in individuals with more mild, localized, or transient pain.

Although a wide range of tests have been used to assess cognitive function in studies of chronic pain populations,<sup>1–6</sup> there does not appear to be a gold standard for such assessments. A systematic review of cognitive function instruments used to assess individuals with chronic pain<sup>35</sup> found that none of the 53 instruments identified had been validated specifically for use in patients with pain, and there was limited

**Table 2** Cognitive function assessments during untreated pain state (Visit 2, pretreatment) relative to pain-free state (Visit 3), mITT population

	Paracetamol 500 mg + caffeine 65 mg (n=6)	Paracetamol 500 mg (n=7)	Placebo (n=7)
<b>Axon Sport – Error-Adjusted Simple Reaction Time, ms<sup>a</sup></b>			
Pain state	n=6	n=7	n=7
Median (range)	0.48 (0.3–0.6)	0.39 (0.3–1.2)	0.44 (0.4–0.8)
Pain-free state	n=6	n=6	n=5
Median (range)	0.36 (0.3–0.6)	0.36 (0.3–0.4)	0.43 (0.4–0.6)
Change (pain vs pain-free)	n=6	n=6	n=5
Median (range)	0.05 (0.0–0.2)	0.07 (0.0–0.8)	0.06 (0.0–0.2)
P-value	0.0625	0.0313 <sup>b</sup>	0.0625
<b>Reaction Time, ms<sup>a</sup></b>			
Pain state	n=6	n=7	n=7
Median (range)	407.75 (389.5–510.0)	427.00 (374.0–592.5)	418.00 (382.5–435.5)
Pain-free state	n=6	n=6	n=5
Median (range)	401.00 (384–511.5)	410.50 (392.0–468.0)	417.00 (399.5–442.0)
Change (pain vs pain-free)	n=6	n=6	n=5
Median (range)	2.00 (–17.5 to 36.0)	–1.75 (–41.0 to 170.5)	–1.00 (–6.5 to 18.5)
P-value	0.5625	0.9999	0.6875
<b>Rapid Visual Information Processing<sup>c</sup></b>			
Pain state	n=6	n=7	n=7
Mean ± SD	0.91±0.037	0.95±0.056	0.91±0.056
Pain-free state	n=6	n=6	n=4
Mean ± SD	0.95±0.020	0.96±0.055	0.93±0.052
Change (pain vs pain-free)	n=6	n=6	n=4
Mean (95% CI)	–0.04 (–0.08 to –0.01)	–0.01 (–0.02 to 0.01)	–0.03 (–0.07 to 0.00)
P-value	0.0227 <sup>b</sup>	0.2785	0.0557
<b>Attention Switching Task, ms<sup>a</sup></b>			
Pain state	n=6	n=7	n=7
Median (range)	62.00 (25.0–74.0)	57.50 (0.0–163.0)	85.00 (55.5–189.0)
Pain-free state	n=6	n=6	n=5
Median (range)	66.25 (18.5–75.5)	43.00 (0.0–77.0)	82.50 (40.5–193.0)
Change (pain vs pain-free)	n=6	n=6	n=5
Median (range)	–3.25 (–44.5 to 46.5)	46.25 (–22.5 to 99.5)	2.50 (–4.0 to 113.5)
P-value	0.9999	0.1563	0.3125
<b>Spatial Working Memory<sup>c</sup></b>			
Pain state	n=6	n=7	n=7
Mean ± SD	35.67±30.32	37.00±29.88	58.43±20.15
Pain-free state	n=6	n=6	n=5
Mean ± SD	45.0±20.86	7.67±5.09	44.00±39.21
Change (pain vs pain-free)	n=6	n=6	n=5
Mean (95% CI)	–9.33 (–29.01 to 10.34)	25.17 (–5.35 to 55.68)	13.80 (–15.99 to 43.59)
P-value	0.2770	0.0875	0.2678
<b>One Touch Stockings of Cambridge<sup>c</sup></b>			
Pain state	n=6	n=7	n=7
Mean ± SD	10.00±2.61	10.71±1.80	12.14±1.77
Pain-free state	n=6	n=6	n=5
Mean ± SD	12.67±1.75	11.17±1.47	12.40±3.05
Change (pain vs pain-free)	n=6	n=6	n=5
Mean (95% CI)	–2.67 (–5.90 to 0.56)	0.00 (–1.15 to 1.15)	–0.20 (–2.42 to 2.02)
P-value	0.0872	0.9999	0.8149

**Notes:** <sup>a</sup>Descriptive summary statistics based on subject-level raw values, analyzed by the nonparametric Wilcoxon signed-rank test. <sup>b</sup>P <0.05 from the parametric two-sided paired t-test for changes from pain state (Visit 2, pretreatment) to pain-free state (Visit 3). <sup>c</sup>Descriptive summary statistics based on subject-level raw values, analyzed by the parametric two-sided paired t-test; 95% CIs for the mean change were calculated for these outcomes only.

**Abbreviations:** CANTAB, Cambridge Neuropsychological Test Automated Battery; mITT, modified intent-to-treat.

**Table 3** Mobility assessments during untreated pain state (Visit 2, pretreatment) relative to pain-free state (Visit 3), mITT population

	Paracetamol 500 mg+ caffeine 65 mg (n=6)	Paracetamol 500 mg (n=7)	Placebo (n=7)
Gait, contact phase, s <sup>a</sup>			
Pain state	n=6	n=7	n=7
Median (range)	0.68 (0.6–0.8)	0.63 (0.6–0.7)	0.73 (0.6–0.8)
Pain-free state	n=6	n=6	n=5
Median (range)	0.64 (0.6–0.8)	0.62 (0.6–0.7)	0.68 (0.6–0.8)
Change (pain vs pain-free)	n=6	n=6	n=5
Median (range)	0.03 (0.0–0.1)	0.02 (0.0–0.1)	0.01 (0.0–0.0)
P-value	0.0313 <sup>b</sup>	0.2188	0.9999
Gait, stride length, cm <sup>c</sup>			
Pain state	n=6	n=7	n=7
Mean ± SD	1.49±0.206	1.53±0.189	1.45±0.147
Pain-free state	n=6	n=6	n=5
Mean ± SD	1.55±0.182	1.62±0.254	1.48±0.194
Change (pain vs pain-free)	n=6	n=6	n=5
Mean (95% CI)	–0.06 (–0.17 to 0.04)	–0.08 (–0.21 to 0.05)	–0.02 (–0.07 to 0.02)
P-value	0.1708	0.1568	0.2321
Gait, walking speed, m/s <sup>a</sup>			
Pain state	n=6	n=7	n=7
Median (range)	1.36 (1.2–1.8)	1.46 (1.3–1.8)	1.34 (1.1–1.6)
Pain-free state	n=6	n=6	n=5
Median (range)	1.48 (1.2–1.9)	1.62 (1.3–2.0)	1.42 (1.1–1.7)
Change (pain vs pain-free)	n=6	n=6	n=5
Median (range)	–0.10 (–0.3 to 0.0)	–0.15 (–0.3 to 0.2)	–0.03 (–0.1 to 0.1)
P-value	0.0625	0.3125	0.4375
Time to stand, s <sup>a</sup>			
Pain state	n=6	n=7	n=7
Median (range)	1.28 (1.1–1.4)	1.28 (1.0–1.6)	1.37 (1.0–1.7)
Pain-free state	n=6	n=6	n=5
Median (range)	1.18 (1.0–1.7)	1.18 (1.0–1.3)	1.17 (1.0–1.4)
Change (pain vs pain-free)	n=6	n=6	n=5
Median (range)	0.10 (–0.4 to 0.2)	0.13 (–0.2 to 0.3)	0.09 (0.0–0.3)
P-value	0.4375	0.3125	0.1250
Time to stand, ground reaction force, newtons <sup>c</sup>			
Pain state	n=6	n=7	n=7
Median (range)	624.35 (585.2–822.5)	685.33 (490.0–812.6)	715.19 (553.1–976.4)
Pain-free state	n=6	n=6	n=5
Median (range)	616.04 (591.4–831.9)	669.31 (490.8–919.6)	727.38 (542.5–976.7)
Change (pain vs pain-free)	n=6	n=6	n=5
Median (range)	2.53 (–9.4 to 21.6)	–5.35 (–107.0 to 10.1)	3.21 (–12.2 to 17.3)
P-value	0.5166	0.3184	0.4960
Grip force, kg <sup>c</sup>			
Pain state	n=6	n=7	n=7
Mean ± SD	27.67±9.145	26.07±8.935	33.90±7.212
Pain-free state	n=6	n=6	n=5
Mean ± SD	29.65±10.043	30.07±11.179	35.88±10.098
Change (pain vs pain-free)	n=6	n=6	n=5
Mean (95% CI)	–1.98 (–7.76 to 3.79)	–3.87 (–7.85 to 0.11)	–1.70 (–6.09 to 2.69)
P-value	0.4179	0.0547	0.3426

**Notes:** <sup>a</sup>Descriptive summary statistics based on subject-level raw values, analyzed by the nonparametric Wilcoxon signed-rank test. <sup>b</sup> $P < 0.05$  from the two-sided Wilcoxon signed-rank test for changes from pain state (Visit 2, pretreatment) to pain-free state (Visit 3). <sup>c</sup>Descriptive summary statistics based on subject-level raw values, analyzed by the parametric two-sided paired  $t$ -test; 95% CIs for the mean change were calculated for these outcomes only.

**Table 4** Adverse events (AEs)

	Treatment allocation	Timing relative to treatment administration	Severity	Treatment-related
AEs occurring prior to treatment administration				
Motorbike accident	Paracetamol	21 days before	Mild	No
Common cold/virus	Placebo	26 days before	Moderate	No
Right knee arthralgia	Placebo	11 days before	Mild	No
Common cold/virus	Placebo	18 days before	Mild	No
AEs occurring after treatment administration				
Pharyngeal erythema	Paracetamol	Day of treatment	Mild	No
Worsening hypercholesterolemia	Placebo	10 days after	Mild	No
Acid reflux	Placebo	40 days after	Moderate	No

information in individuals with certain pain types, including musculoskeletal pain. In the current study, we chose the Axon Sports Priming Application and several CANTAB assessments. The CogState simple reaction time test was previously validated against multiple neuropsychological tests in healthy adults aged 35–50 years.<sup>30</sup> To our knowledge, it has not previously been used to assess cognition in studies of patients with pain. However, it was previously validated in and found to be sensitive to mild cognitive impairment among individuals with various neuropsychiatric or neurodegenerative disorders. On that basis, we believe it to be an appropriate tool for use in hypothesis-generating group studies to evaluate the nature and severity of cognitive impairment associated with other diseases/disorders.<sup>30</sup>

The CANTAB combined various tests that had proven useful for neuropsychological testing in animals and humans and converted them into a form that could be administered using digital touch-screen technologies.<sup>36</sup> Thus, it offers the advantages of simple and standardized administration and automated recording of responses with millisecond precision.<sup>7</sup> Although the CANTAB battery of assessments has not been extensively studied in pain conditions, it has been studied in various other neurological conditions, has the advantage of an easy-to-use subject interface, and has been validated in healthy volunteers aged 55–80 years.<sup>28</sup> It was originally designed for use in elderly patients with neurodegenerative diseases (eg, Alzheimer's disease and Parkinson's disease) but has been widely used in other patient populations, including those with various neurologic or psychiatric disorders, brain injury, or developmental disorders.<sup>36</sup> The CANTAB tests we selected for the current analysis focused on the attention and executive function/decision-making domains; these domains were of primary interest to us because we inferred that they might be impacted by pain.

Three previous studies used CANTAB assessments to evaluate cognition in patients with pain conditions, including postherpetic neuralgia,<sup>37</sup> chronic low back pain,<sup>7</sup> and chronic nonmalignant pain treated with opioids.<sup>38</sup> The study in postherpetic neuralgia utilized CANTAB assessments for choice reaction time, semantic memory (Graded Naming Test), decision making (Information Sampling Task), and spatial memory (Stockings of Cambridge test), with impairments seen in all three, but only in patients taking systemic treatments and not in patients taking topical lidocaine therapy compared with age- and sex-matched controls.<sup>37</sup> The study of low back pain used the choice reaction time test, pattern recognition memory test, and the spatial span test of working memory, none of which were found to be affected by pain, although patients using opioid treatment exhibited worsening on the spatial span test compared with healthy controls.<sup>7</sup> The study of patients with opioid-tolerant chronic nonmalignant pain used the rapid visual information processing test of general cognitive performance, as well as the tests for spatial recognition memory and spatial working memory, but focused on whether taking oxycodone extended release with a high-fat meal vs a fasted state affected these cognitive outcomes; it was not designed to assess the impact of pain or opioid therapy on cognition.<sup>38</sup>

## Conclusion

The substantial limitations of this study relating to the small sample size and the breach in data transmission protocol prevent accurate interpretation of the current results and leave the central study questions regarding the effects of pain on cognitive function and mobility unanswered. However, the design of the current study remains pertinent as a model for development of future investigations into these important questions. For future studies, there is strong rationale



for pursuing the effects of pain on attention and executive function/decision-making capability, as there seems to be evidence for overlap in the neural regions responsible for pain sensation and cognition, resulting in competition for resources.

## Abbreviations

AE, adverse event; BPI, Brief Pain Inventory; CANTAB, Cambridge Neuropsychological Test Automated Battery; GSKCH, GlaxoSmithKline Consumer Healthcare; ITT, intent-to-treat; mITT, modified intent-to-treat.

## Data sharing statement

Anonymized individual participant data and study documents can be requested for further research from [www.clinicalstudydatarequest.com](http://www.clinicalstudydatarequest.com).

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## Author contributions

Both authors were actively involved in preparing this paper for publication and made substantial contributions to: 1) the conception and design of the study, or acquisition of the data, or analysis and interpretation of the data; and 2) drafting the article or revising it critically for important intellectual content. Moreover, they have each 3) granted final approval of the current version for submission to be published and 4) agree to be accountable for all aspects of the work.

## Disclosure

Sebastian A Moreira and Petr Novak are employees of GlaxoSmithKline Consumer Healthcare. The authors report no other conflicts of interest in this work.

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