ORIGINAL ARTICLE

Validation of the Bowel Function Index to detect clinically meaningful changes in opioid-induced constipation

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Abstract

Objective: The Bowel Function Index (BFI) is a clinician-administered, patient-reported, 3-item questionnaire to evaluate opioid-induced constipation in cancer and non-cancer chronic pain patients. The objective of the present analysis was to evaluate the psychometric characteristics of the BFI using data from clinical studies of oral prolonged release (PR) oxycodone/naloxone.

Methods: OXN2401 was a multicenter, controlled, randomized, double-blind, parallel-group study including oral PR oxycodone combined with oral PR naloxone as well as oral PR oxycodone combined with corresponding naloxone placebo. OXN3401 and OXN3001 were 12-week multicenter, controlled, randomized, double-blind, parallel-group studies of a fixed combination of oral PR oxycodone/naloxone versus PR oxycodone. In addition, a placebo group was included in study OXN3401. BFI psychometric characteristics (reliability, reproducibility, convergent/known groups validity, and responsiveness) were evaluated.

Results: Demographic data ($n=985$) were comparable and analyses indicated a high degree of internal consistency (Cronbach's alpha >0.7). Change of less than 5 points in BFI was indicative of high reproducibility. Correlations between BFI item and total scores to stool frequency were statistically significant and in the low-to-moderate range (OXN2401 –0.23 to –0.29, $p < 0.001$; OXN3401 range –0.26 to –0.40, $p < 0.001$; OXN3001 –0.14 to –0.15, $p < 0.05$). Data indicate that a BFI score change of ≥12 points represents a clinically meaningful change in constipation.

Limitations: This publication for validation of BFI only includes data from three clinical trials. However, another publication of an additional specifically designed cross-sectional validation study is in preparation.

Conclusion: The BFI is a valid and reliable instrument for the assessment of opioid-induced constipation in chronic pain patients. Psychometric analyses from clinical trials support the BFI's psychometric properties.

Key words: *Bowel Function Index, opioid-induced constipation, pain, patient-reported outcomes*

Introduction

Opioids are established for the treatment of chronic pain patients. However, opioid therapy is frequently related with opioid-induced bowel dysfunction (OIBD)[1], the most significant and therefore treatment-limiting adverse side-effect. In fact, a recent study shows that approximately 30% of patients reduce or terminate treatment with opioids as a result of OIBD[2,3].

Implying a spectrum of opioid induced gastrointestinal (GI) effects, OIBD is a consequence of opioid binding to µ- and κ-opioid receptors[4] resulting in reduced, dyscoordinated muscle contraction and reduced GI secretions[5-8]. As a result, OIBD comprises hard dry stools, straining, bloating, abdominal cramping, abdominal distension, increased gastric reflux, incomplete bowel evacuation and as the most distressing lead symptom opioid-induced constipation (OIC)[1,2]. Whereas many of the other known side-effects of opioids (e.g., nausea, sedation or itching) subside with long-term use, OIC often persists and therefore has to be managed to ensure and improve patients' compliance and quality of life[3,9].

Traditional management strategies of OIC have been nonspecific and often ineffective[10] as they were

not targeting the underlying opioid-receptor mediated mechanisms[1,3]. A typical treatment option is laxatives[1,12], but all are associated with side-effects and treat the consequences of opioid therapy rather than the cause, therefore failing optimal treatment results[1]. To overcome OIC, a range of compounds have been developed that target peripheral opioid receptors in the GI tract including alvimopan[13,14], methylnaltrexone[15] and oral prolonged release (PR) naloxone combined with the oral PR opioid oxycodone[15-17]. The lack of validated outcome measures has been a limitation when evaluating the efficacy of treatments that alleviate symptoms associated with OIC[18]. Similarly, it has been difficult to quantify GI side-effects of opioids.

Hence, it is very important to have an easy-to-use patient-reported outcome (PRO) tool to evaluate the severity and impact of OIC. A PRO is a measure of a patient's health status that comes directly from the patient, without interpretation by a clinician. In clinical trials, a PRO instrument is used to measure the impact of an intervention on aspects of patients' health status, and can be unidimensional (e.g., measuring symptoms such as headache or constipation) or multi-domain concepts with physical, psychological, and social components[19]. Data generated by a PRO instrument can provide evidence of a treatment benefit from the patient perspective, but requires evaluation to ensure it is a reliable and valid measure.

Indeed, there are already objective measurements that can partly detect parameters like stool frequency and stool consistency[20], but from the patient's point of view the quality aspects like severity and impact are not captured through these parameters. For a comprehensive assessment, this points out the need to draw on objective and even more important subjective criteria. Although respective subjective rating scales for OIC are already described[21,22], there is still a lack of validated easy-to-use methods to specifically assess OIC. To have a subject assessment for bowel function with focus on OIC, a specific rating scale the Bowel Function Index (BFI) has been developed.

The development of the BFI was based on established criteria of known assessment tools for OIC. It is a subjective rating scale consisting of three items captured by a numeric analogue scale (NAS; 0-100) an important point as the main target group is chronic pain patients who are in general familiar with NAS for the assessment of pain. Along with the fact that the BFI is focused on the three main concepts for measuring OIC, it is an easy-to-use tool contributing to the simplification and harmonization of symptom assessment in this patient group.

The symptoms ease of defecation (straining), incomplete bowel evacuation and the general judgment of constipation are also established in the Rome criteria[23] and other questionnaires like the PAC-SYM (Patient Assessment of Constipation Symptoms)[21,22], although use of these tools may not be practical for daily use in the clinical setting.

The Bowel Function Index (BFI) has been developed to assess clinical symptoms of opioid-induced constipation. It is patient-assessed and clinician-administered and intended to be easy to use to reduce burden on patients. In this analysis the BFI was evaluated using data from three clinical trials for the combination of PR oxycodone and PR naloxone. For validation purpose of the BFI, selected subjective (e.g., PAC-SYM) and also clinical characteristics like stool consistency, stool frequency, and in particular complete spontaneous bowel movements (CSBM) were used. The objective was to evaluate the psychometric characteristics of the BFI in patients with opioid-induced constipation. We report on the reliability and validity and responsiveness of the BFI total and item scores.

Methods

Data to psychometrically evaluate the BFI scale were derived from three clinical studies of oral PR oxycodone administered with oral PR naloxone[17,24-26]. All studies were multicenter, prospective, randomized, double-blind, parallel-group studies. Each study was conducted in accordance with the Declaration of Helsinki (1964) and its successors (Edinburgh, 2000 and Washington, 2002) and complied with the principles of Good Clinical Practice (GCP) set by the International Conference on Harmonization (ICH) and applicable German regulatory requirements. Written informed consent was obtained from patients at screening. Male and female patients aged more than 18 years were eligible to take part in the studies if they were experiencing moderate-to-severe chronic pain, as assessed by the investigator. Exclusion criteria included current alcohol or drug abuse, current acute pancreatitis, current severe cardiovascular or respiratory diseases (e.g., lung cancer or metastases), current severe renal or liver impairment (transaminase levels three times above normal range), liver or renal carcinoma or metastases. Details of the design of these studies, including statistical analyses and overview of patient populations, can be found elsewhere[17,24-26].

Study designs

The purpose of the clinical studies was to assess the efficacy of PR naloxone combined with PR oxycodone. The purpose of the two studies OXN2401 and OXN3001 was to assess the efficacy of naloxone combined with oxycodone on bowel function as measured by the BFI. In addition, study OXN3401 was also drawn on for this purpose. Although the primary focus was the evaluation of analgesic efficacy, the assessment of the BFI was one
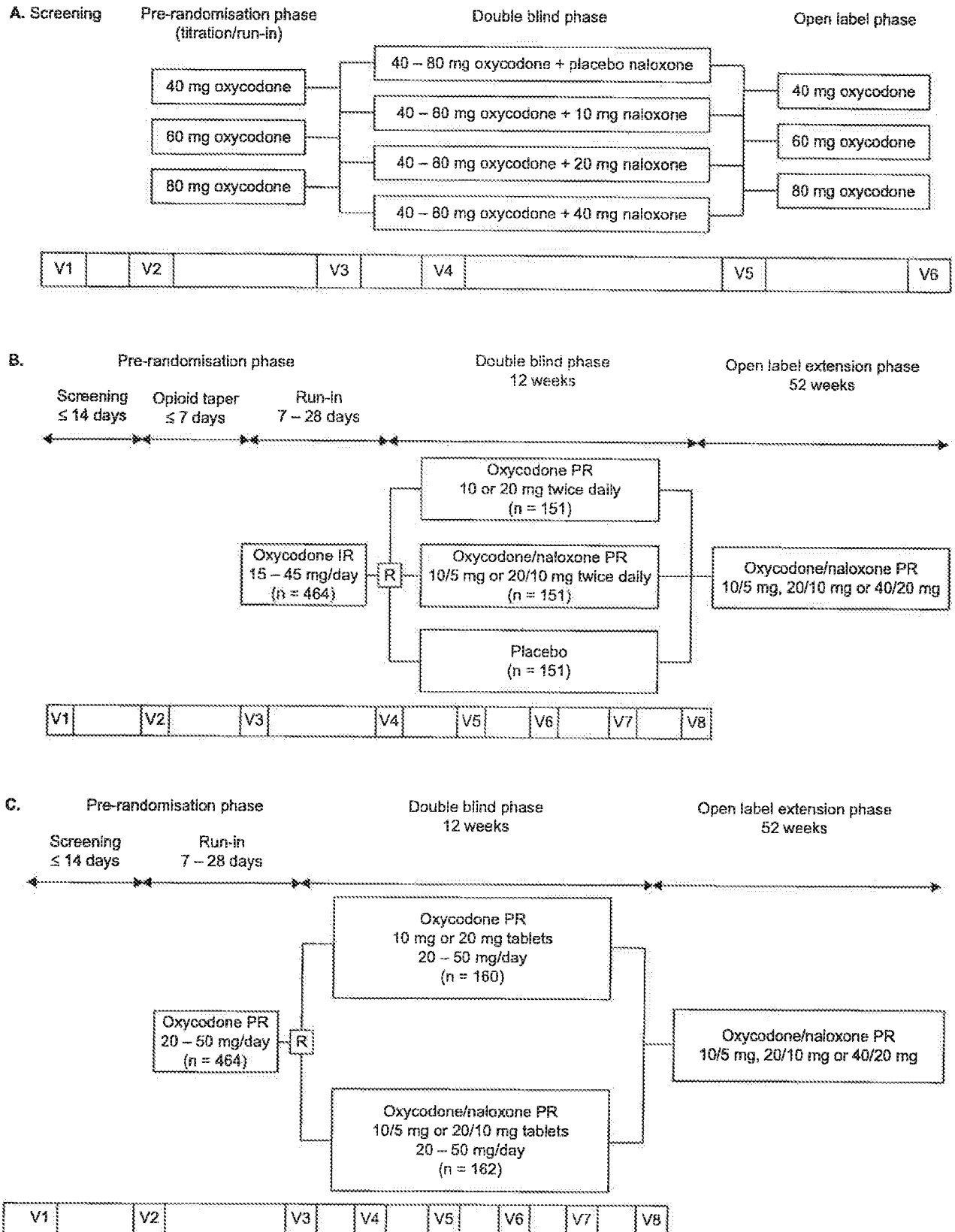
Figure 1. Overview of study design. (a) Study OXN2401: six study visits (V1-V6) were undertaken over the course of up to 10 weeks. (b) Study OXN3401. (c) Study OXN3001 (R = Randomization).

of the secondary endpoints. The psychometric analyses described in this publication were not designed to evaluate the treatment effects of PR oxycodone plus oral PR naloxone compared with placebo. This report only describes the methods and results of a blinded evaluation of the psychometric qualities of the BFI assessed during the screening and double-blind phase of the three clinical trials.

Each study had three phases: pre-randomization (which consisted of screening and titration/run-in), a double-blind treatment period (maintenance phase), and an open-label phase (Figure 1a–c).

The OXN2401 clinical trial was a multicenter, prospective, controlled, randomized, double-blind, four parallel group phase II study of oral PR oxycodone plus oral PR naloxone (three different dose groups) and oral PR oxycodone plus naloxone placebo in subjects with severe chronic pain (Figure 1a)[17]. The OXN3401 phase III trial was a 12-week multicenter, randomized, double-blind, placebo- and active-controlled, double-dummy parallel group trial of the safety and efficacy of PR oxycodone/naloxone tablets in subjects with moderate-to-severe, chronic non-malignant low back pain (Figure 1b)[25]. The OXN3001 clinical trial was a phase III, 12-week multicenter, randomized, double-blind, double-dummy, parallel-group clinical trial evaluating PR oxycodone/naloxone tablets compared to PR oxycodone alone in patients with moderate-to-severe, chronic, non-malignant pain reporting the presence of opioid-induced constipation (Figure 1c)[26].

Bowel Function Index (BFI)

The BFI is a clinician administered, patient-reported 3-item questionnaire measuring the level of bowel function focusing on constipation a patient is experiencing (Figure 2). It evaluates constipation from the patient's perspective. The patient assesses the severity of each component using a 0–100 numerical rating scale where 0 = no problems, and 100 = most severe problems (Figure 2).
The components of the BFI are:

* Ease of defecation
* Feeling of incomplete bowel evacuation
* Patient's personal judgment of constipation
* The patient rates his/her perception of each component from his/her experience over the preceding 7 days

All randomized patients who received study medication and completed any of the three BFI questions were evaluated. An overview of data collection points is shown in Table 1a–c. For each study, the sociodemographic data were collected at visit 1 (Figure 1a–c) and pre-treatment data were collected at visit 3. Data collected at visit 5 (OXN2401),

visit 6 (OXN3001), or visit 8 (OXN3401) compared with the baseline values at visit V3 (OXN2401), V4 (OXN3401) and V3 (OXN3001) were used as endpoints assessing bowel efficacy (Figure 1a–c). In studies OXN2401 and OXN3401, data from the period between visit 5 and visit 6 were used as retest data; in study OXN3001 data from visit 1 to visit 2 were used. In all cases it was assumed that data stability at these points would be greatest due to stability of interventions in the studies at these time points.

Bowel function measures

In all three studies, the bowel function measures were completed by patients in daily diaries. The bowel function measures included stool frequency assessed by number of complete spontaneous bowel movements (CSBM in OXN3001), or bowel evacuations per day (OXN2401, OXN3401), stool consistency as measured by the Bristol Stool Form Scale (OXN3001) and the Likert Scale (OXN2401, OXN3401), the frequency of laxative use (OXN3001), the number of days with laxative use (OXN2401) or the number of days of laxative use prior to each bowel movement (OXN3401), and stool completion (OXN3401 and OXN3001). Tables 1a–c give an overview of the study designs of the three studies including the bowel function measures. The data were used to validate the BFI.

Data sets analyzed

All patients randomized in each study who received study medication and completed any of the three BFI questions were evaluated. Baseline data (visit 3 in OXN2401 and OXN3001, visit 4 in OXN3401) and endpoint data (visit 5 in OXN2401, visit 6 in OXN3001, visit 8 in OXN3401) were used (Figure 1a–c). Data from the period between visit 5 and visit 6 (study OXN2401 and OXN3401) and visit 1 and visit 2 (study OXN3001) were used as test-retest data as it was assumed that data stability at this point would be greatest because of the consistency of therapeutic interventions at these points – double-blind phase in studies OXN2401 and study OXN3401 and opioid run-in phase for study OXN3001.

Statistics

Descriptive statistics are reported on sociodemographic (age, gender, race) and clinical variables (daily pain intensity [average pain], stool frequency, stool consistency, and number of days of laxative intake). Mean, standard deviation, and range were calculated for continuous variables and frequency was calculated for categorical

Bowel Function Index (BFI): Instructions for use
Instructions for study personnel on the administration of the BFI to study subjects

The Bowel Function Index (BFI) is a 3-item questionnaire to measure constipation from the patients perspective. Study personnel should ask subjects the BFI questions. The BFI is not intended to be given to the subject for completion on their own (self-administration), not even if study personnel explain how the measure should be completed. The BFI should always be administered to the subject by study personnel.

> Instructions for administering each item of the BFI are indicated in the grey sections below each item.

Ask subjects each question. If the subject does not understand the question, study personnel may provide clarification as indicated below each question in the grey sections of the measure below. Study personnel should enter each answer provided by the subject in the appropriate section of the case record form (CRF). To avoid any form of response bias, study personnel must not lead the subjects in their answers (e.g. study personnel should not provide examples of answers to a given question).

Bowel Function Index (BFI)

Please complete all items in this assessment

1. Ease of defecation (NAS) during the last 7 days according to patient assessment:

   0 = easy / no difficulty
   100 = severe difficulty

Ask the subject: "During the last 7 days, how would you rate your ease of defecation on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?"

If the subject requires clarification, ask: "During the last 7 days, how easy or difficult was it to have a bowel movement on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?"

2. Feeling of incomplete bowel evacuation (NAS) during the last 7 days according to patient assessment:

   0 = not at all
   100 = very strong

Ask the subject: "During the last 7 days, how would you rate your feeling of incomplete bowel evacuation on a scale from 0 to 100, where 0 = no feeling of incomplete evacuation and 100 = a very strong feeling of incomplete evacuation?"

If the subject requires clarification, ask: "During the last 7 days, how strongly did you feel that you did not empty your bowels completely? Please indicate how strong this feeling was on a scale from 0 to 100, where 0 = not at all and 100 = very strong"

3. Personal judgement of patient (NAS) regarding constipation during the last 7 days:

   0 = not at all
   100 = very strong

Ask the subject: "During the last 7 days, how would you rate your constipation on a scale from 0 to 100, where 0 = not at all and 100 = very strong"

If the subject requires clarification, ask: "During the last 7 days, how would you rate how constipated you felt on a scale from 0 to 100, where 0 = not at all and 100 = very strong"

Figure 2. The Bowel Function Index (BFI) tool. The BFI is a 3-item questionnaire to measure constipation from the patient's perspective. It is intended to be used by healthcare professionals to question patients and should not be used for patient self-administration.

Table 1a. Overview of patient visits and questionnaire completion by participants in study OXN2401.

Study phase	Pre-randomization		Double-blind phase			Follow-up*
Study period	Screening	Run-in				
Visit	V1	V2	V3	V4	V5	V6
Duration	≤14 days	≤21 days				
Study day			1	8	28	42
BFI		x	x	x	x	x
BFM†		x	x	x	x	x

*With oxycodone only; †Bowel function measures including stool frequency (bowel evacuations per day), stool consistency and laxative intake (number of days with laxative use).

Table 1b. Overview of patient visits and questionnaire completion by participants in study OXN3401.

Study phase	Pre-randomization		Double-blind			
Study period	Screening opioid taper	Run-in				
Visit	V1-V3	V3-V4	V5	V6	V7	V8
Duration	14 days	14 days				
Study day			14	28	56	84
BFI		x	x	x	x	x
BFM*		x	x	x	x	x

*Bowel function measures including stool frequency (bowel evacuations per day), stool consistency, laxative intake (number of days of laxative intake prior to each bowel movement), stool completion and evaluation of the completeness of the bowel movement).

Table 1c. Overview of patient visits and questionnaire completion by participants in study OXN3001.

Study phase	Pre-randomization		Double-blind phase				
Study period	Screening	Run-in*					
Visit	V1	V2 - V3	V4	V5	V6	V7	V8
Duration	≤14 days	≤14 days					
Study day		1	8	15	29	57	85
BFI	x	x	x	x	x	x	x
PAC-SYM	x	x	x	x	x	x	x
BFM†		x	x	x	x		

*Run-in phase with immediate release oxycodone (7-28 days); †Bowel function measures including stool frequency (number of complete spontaneous bowel movements, stool consistency, laxative intake (number of days of laxative intake prior to each bowel movement), stool completion and evaluation of the completeness of the bowel movement for the first 4 weeks.

variables. The sociodemographic and clinical variables were used to characterize the sample and quantify constipation severity. To evaluate the performance of each item of the BFI scale, descriptive statistics of each BFI item and BFI total score were undertaken at visit 3 and visit 5 (study OXN2401)[17], visit 6 (OXN3001) and visit 8 (OXN3401)[25]. Patients were stratified into three severity levels (mild, moderate, severe).

Analyses of BFI item, mean total BFI score and severity of opioid-induced constipation were evaluated using an analysis of co-variance (ANCOVA) with severity being determined using a 4-point response scale in OXN2401 and OXN3401 (hard, solid, semi-solid, watery) in OXN2401 and OXN3401 and the well-established 7-point Bristol Stool Form Scale in OXN3001[26].

The Bristol Stool Form Scale was recoded to match the stool consistency data collected in OXN2401 and OXN3401: type 1 for the Bristol Stool Form Scale was 'hard' (= 1), types 2 and 3 were 'solid' (= 2), types 4 and 5 were 'semi-solid' (= 3), and types 6 and 7 'watery' (= 4). If the median was located between two values, the worst case was selected for use in the analysis.

Reliability and validity

Internal consistency was evaluated using Cronbach's alpha for the BFI total score using data from the period before the randomization visit (visit 2 in study OXN2401 and visit 3 in studies OXN3401 and OXN3001)[27,28]. Values range from 0 to 1.0, and higher values indicate an increasingly reliable, homogeneous instrument with good reliability (i.e., ≥0.7). Inter-item reliability was evaluated using methods of Cohen *et al*[29] as correlations of 0.4 or less are indicative of poor correlation. Test–retest reliability was explored using data from the naloxone plus placebo group and the interval from visit 5 to visit 6 as the retest interval using intra-class correlation (ICC) coefficients, Pearson's correlations and change in score[30].

In study OXN2401, convergent validity, the relationship between BFI questions and total BFI score and clinical characteristics of stool frequency, number of days of laxative use and global assessment of tolerability, were analyzed using Spearman's rank correlations[31]. Known-groups validity was analyzed using ANCOVA models to compare BFI item and total scores based on visit 5 data[32]. Patients were stratified into the three severity groups of mild, moderate and severe based on patient diary data and stool consistency data. In studies OXN3401 and OXN3001, convergent validity was evaluated through calculations of Spearman's product-moment range correlations[31,32] between each BFI item and BFI total score and a series of clinical outcomes including stool frequency and consistency, and number of days of laxative intake. In study OXN3001, correlations with the Patient Assessment of Constipation Symptoms (PAC-SYM), a subjective outcome measure, were also undertaken. The PAC-SYM questionnaire is a 12-item self-report instrument divided into abdominal, rectal and stool domains[21,22]. All correlations were explored using visit 3 data. In study OXN3401 correlations with complete spontaneous bowel movements (CSBM) were undertaken using visit 8 data.

Responsiveness

Responsiveness refers to the extent to which the BFI scale can detect true changes in patients with opioid-induced constipation as outlined by Hays and Revicki 2005[33]. In these studies effect size was determined from individual BFI item and total scores by dividing the mean visit 3 to visit 5 (OXN2401), visit 6 (OXN3001) and visit 8 (OXN3401) score change by the standard deviation (SD) of BFI at visit 3. The effect size was characterized as small, moderate or large according to Cohen *et al*[29].

Two further methods for determining responsiveness were undertaken. The first was the standard error of measurement (SEM) which has been proposed as a useful distribution-based statistic for evaluating clinically meaningful change in health-related quality of life measures[34,35]. The SEM was calculated for all patients based on visit 3 BFI total score and Cronbach's alpha. The second method was that of half standard deviation (SD)[12], to quantify clinically significant BFI score changes at visit 3. The SEM and one-half SD methods are supportive of one another in quantifying clinically meaningful changes.

Results

There were 985 evaluable patients included in this secondary analysis validation study (Table 2). Patients were evenly matched in each study in terms of age (ranged from 56 to 59 years). Across all three studies females predominated with over 60% of the sample.

In all three studies, the BFI total scores demonstrated a high internal consistency, with Cronbach's alpha above 0.7 (range 0.87–0.91; Table 3). The highest correlations (range 0.79–0.86) were between ease of defecation and patient personal judgment compared with other BFI items; correlations were slightly lower (range 0.59–0.75) for assessments of feeling of incomplete evacuation (Table 3).

Reproducibility in studies OXN2401 and OXN3401 was examined using data from patients receiving placebo naloxone from visit 5 to visit 6 (Table 4a), and secondarily from patients receiving placebo naloxone but who reported no change in symptoms (Table 4b–c). For OXN3001 (Table 4d) the data of the entire sample between visit 1 and visit 2 was used since it is expected that the patients are stable during the respective periods (screening and run-in). It is clear that mean differences in BFI score from visit 5 to visit 6 differ less than 5 points, which was not statistically significant, indicative that BFI scores were stable over a test–retest period. For the secondary analysis of patients receiving placebo naloxone who also experienced no change in symptoms patient numbers are low in study OXN2401 (*n*=12) which limits interpretation of results. However, in study OXN3401 patients randomized to placebo numbered 135; mean differences

Table 2. Demographic information / clinical parameters of patients included in the study.

Characteristic	Mean parameter		
	Study OXN2401 *n*=202	Study OXN3401 *n*=460	Study OXN3001 *n*=323
Age years*	56.3 (13.1)	56.4 (11.0)	58.7 (12.0)
Gender			
Female	127 (62.9%)	284 (61.7%)	195 (60.4%)
Male	75 (37.1%)	176 (38.3%)	128 (39.6%)
Stool consistency (Likert scale 1-4)**	2.5	3.0	2.0§
Stool consistency†			
Hard	NE	55 (10.2%)	25 (7.7%)
Solid	NE	153 (28.3%)	182 (56.3%)
Semi-solid	NE	299 (55.4%)	88 (27.2%)
Watery	NE	33 (6.1%)	17 (5.3%)
Laxative intake†	6.0 (1.9)	13.5 (33.7)	NE

NE, not evaluated; †(*n*[%]); ‡(mean no. of days [SD]); *mean [SD]; **Likert scale (median values according to patients' diaries) with hard = 1, solid = 2, semi-solid = 3 and watery =4; §Stool consistency was originally measured by the Bristol Stool Form Scale. To match the stool consistency data collected in OXN2401 and OXN3401, the respective 7-point response scale was recoded to a 4-point scale. If the median value was located between two values, the worst case was selected for use in the analysis.

from visit 5 to visit 6 were <2 points and were not significantly different, again suggesting stability of the BFI score between the time points. Similarly, in study OXN3001, whilst reproducibility was examined on the entire patient population at visit 1 (screening) and visit 2 (run-in), BFI item and mean total scores remained stable with <2 points difference between the timepoints.

Stability and reproducibility were further explored across all studies using Pearson's product-moment and ICC correlations. In each study it was clear that the ICC coefficients and Pearson's correlations were in the moderate-to-large range and were statistically significant (p < 0.001).

When patients were stratified according to severity of their constipation it was evident that BFI scores were higher for those classified as severely constipated compared with those classified as moderately constipated (Table 5). BFI scores also differed between those patients classified as mildly constipated compared with those classified as severe. BFI in those classified as moderately constipated was not always higher than in those classified as mildly constipated (Table 5).

In all studies, correlations between individual BFI items and mean total score to clinical characteristics of stool frequency/consistency, number of days of laxative use and CSBM were examined using Spearman's rank order correlation (Table 6). Correlation between BFI item and total scores to stool frequency were inverse, in the

Table 3. Correlations between each BFI item and internal consistency across studies OXN2401 (*n*=202), OXN3401 (*n*=460) and OXN3001 (*n*=323).

BFI item	Ease of defecation	Feeling of incomplete bowel evacuation	Judgment regarding constipation	Total score	Cronbach's alpha
Ease of defecation					
OXN2401	1.00	0.59*	0.86*	0.91*	
OXN3401	1.00	0.75†	0.82†	0.96†	
OXN3001	1.00	0.64*	0.79*	0.89*	
Feeling of incomplete bowel evacuation					
OXN2401		1.00	0.60*	0.84*	
OXN3401		1.00	0.7†	0.87†	
OXN3001		1.00	0.70*	0.87*	
Judgment regarding constipation					
OXN2401			1.00	0.91*	
OXN3401			1.00	0.88†	
OXN3001			1.00	0.91*	
Total score					
OXN2401				1.00	0.87
OXN3401				1.00	0.91
OXN3001				1.00	0.88

*$p < 0.001$; †$p < 0.0001$.

Table 4. Reproducibility of BFI items visit 5 to visit 6 for patients randomized to (a) placebo and (b) those subjects who had no change in stool frequency between visit 5 and visit 6 in study OXN2401 (c) those subjects who had no change in stool frequency between visit 5 and visit 6 in study OXN3401 (d) entire subject group in study OXN3001 between visit 1 and visit 2.

(a) Patients randomized to placebo.

	Mean BFI visit 5 (SD)	Mean BFI visit 6 (SD)	Difference	ICC	Pearson's correlation (*r*)
Ease of defecation					
OXN2401 (*n*=43)	49.5 (24.2)	52.7 (27.5)	3.1	0.53	0.53*
OXN3401 (*n*=135)	19.4 (23.0)	20.9 (22.5)	1.48	0.80	0.80*
Feeling of incomplete bowel evacuation					
OXN2401 (*n*=43)	37.0 (19.3)	41.7 (27.5)	4.6	0.72	0.72*
OXN3401 (*n*=135)	20.4 (22.9)	19.1 (22.6)	−1.26	0.77	0.77*
Judgment regarding constipation					
OXN2401 (*n*=43)	49.9 (26.2)	53.5 (26.4)	3.6	0.63	0.63*
OXN3401 (*n*=135)	14.4 (22.7)	15.0 (24.4)	0.59	0.79	0.79*
Total score					
OXN2401 (*n*=43)	45.6 (22.5)	50.0 (24.4)	4.4	0.64	0.65*
OXN3401 (*n*=135)	18.0 (21.2)	18.3 (21.3)	0.27	0.85	0.85*

*$p<0.001$.

(b) Data for stable patients – study OXN2401 (*n*=12).

	Mean BFI visit 5 (SD)	Mean BFI visit 6 (SD)	Difference	ICC	Pearson's correlation (*r*)
Ease of defecation	48.3 (18.0)	50.8 (23.5)	2.5	0.29	0.28
Feeling of incomplete bowel evacuation	31.7 (22.1)	40.4 (21.6)	8.8*	0.82	0.88*
Judgment regarding constipation	49.2 (17.3)	50.4 (24.7)	1.3	0.14	0.14
Total score	43.1 (15.0)	47.2 (21.5)	4.2	0.49	0.51

*$p<0.001$.

(c) Data for stable patients – study OXN3401 (*n*=120)

	Mean BFI visit 5 (SD)	Mean BFI visit 6 (SD)	Difference	ICC	Pearson's correlation (*r*)
Ease of defecation	20.7 (22.0)	20.0 (20.7)	–0.67	0.71	0.71*
Feeling of incomplete bowel evacuation	19.7 (22.6)	16.5 (19.2)	–3.17	0.65	0.66*
Judgment regarding constipation	15.1 (21.3)	13.8 (20.5)	–1.25	0.63	0.63*
Total score	18.5 (20.5)	16.8 (18.6)	–1.69	0.7	0.70*

*p=0.001.

(d) Data for patients in study OXN3001

	Mean BFI visit 1 (SD)	Mean BFI visit 2 (SD)	Difference	ICC	Pearson's correlation (*r*)
Ease of defecation	60.1 (24.3)	60.4 (22.7)	0.34	0.64	0.64*
Feeling of incomplete bowel evacuation	54.1 (27.4)	55.9 (27.0)	1.77	0.62	0.62*
Judgment regarding constipation	59.2 (25.5)	58.6 (24.9)	–0.55	0.63	0.62*
Total score	57.8 (22.5)	58.6 (24.9)	0.51	0.63	0.62*

*p=0.001.

Table 5. Determining known-groups validity of the BFI tool, constipation severity based on stool consistency (ANCOVA analysis).

	Mild	Moderate	Severe	Overall *F*-value
Ease of defecation				
OXN2401	36.6 (28.1)	36.0 (22.3)	58.5 (24.6)	5.88*
OXN3401	21.1 (1.3)	28.1 (1.9)	38.6 (5.3)	50.5†
OXN3001	33.7 (2.0)	48.3 (2.5)	62.3 (6.9)	15.6†
Feeling of incomplete bowel evacuation				
OXN2401	27.2 (26.9)	24.9 (22.0)	53.6 (26.3)	7.00*
OXN3401	20.1 (1.3)	23.5 (1.8)	34.1 (5.2)	39.5†
OXN3001	34.7 (2.1)	45.6 (2.7)	62.7 (7.5)	20.0†
Judgment regarding constipation				
OXN2401	35.3 (30.1)	34.0 (22.4)	57.9 (27.1)	5.02*
OXN3401	15.3 (1.3)	22.8 (1.9)	28.5 (5.4)	49.9†
OXN3001	30.8 (2.0)	44.5 (2.6)	61.4 (7.1)	22.1†
Total score				
OXN2401	33.0 (25.3)	31.6 (19.5)	56.8 (24.9)	7.40*
OXN3401	18.8 (1.2)	24.7 (1.7)	33.6 (4.8)	55.9†
OXN3001	33.1 (1.9)	46.1 (2.4)	61.9 (6.5)	22.0†

*p<0.01; †p<0.001.

Table 6. Spearman's rank order correlations of BFI items and clinical data of stool consistency, frequency and number of days the patients received laxatives in studies OXN2401, OXN3401 and OXN3001*.

	Stool frequency	Stool consistency	No. of days laxatives received	Patient rated assessment of global tolerability
Ease of defecation				
OXN2401	–0.28	–0.23	0.42	0.23
OXN3401	–0.40	–0.18	0.43	NE
OXN3001	–0.27	–0.18	0.19	NE
Feeling of incomplete bowel evacuation				
OXN2401	–0.23	–0.26	0.33	0.34
OXN3401	–0.26	–0.08	0.39	NE
OXN3001	–0.45	–0.07	0.16	NE
Judgment regarding constipation				
OXN2401	–0.28	–0.28	0.44	0.29
OXN3401	–0.39	–0.17	0.44	NE
OXN3001	–0.28	–0.17	0.28	NE
Total score				
OXN2401	–0.29	–0.24	0.45	0.31
OXN3401	–0.37	–0.15	0.43	NE
OXN3001	–0.36	–0.15	0.22	NE

NE, not evaluated; *Stool frequency for OXN3001 was calculated from complete spontaneous bowel movement (CSBM).

low-to-moderate range and statistically significant (study OXN2401 range –0.23 to –0.29, *p* < 0.001; study OXN3401 range –0.26 to –0.40, *p* < 0.001; study OXN3001 using CSBM range –0.27 to –0.45, *p* < 0.01). Similar observations were seen for stool consistency, albeit slightly lower (Table 6). In all studies, the number of days a patient received laxatives positively and moderately correlated with each BFI item and BFI total score. In

studies OXN2401 and OXN3401 ease of defecation and personal judgment of constipation demonstrated a statistically significant correlation with the number of days receiving laxatives, exceeding 0.40 (Table 6). However, the correlation observed for feelings of incomplete

evacuation was lower ($r≤0.39$), suggesting that perceptions of defecation and personal judgment are more related to laxative intake than feelings of evacuation (Table 6). In study OXN3001 BFI score correlated moderately with PAC-SYM data (range 0.38–0.66, $p < 0.001$).

In study OXN2401, improvements in each BFI parameter: defecation, complete evacuation and personal judgment of constipation, with respect to effect size increased with increasing dose of naloxone, indicative of increasing responsiveness (Figure 3a). In this study, effect size changes were typically greater than 0.5 or 0.8 indicative of a moderate or large change as a result of treatment, respectively. Similarly, in study OXN3001 effect sizes were all large (range 0.76–0.88) (Figure 3b). By contrast, the effect sizes in study OXN3401 were all small which is perhaps not surprising as analyses were conducted on the entire study population including patients receiving non-constipating placebo (Figure 3b). In all studies effect size was greatest for the parameters of defecation and personal judgment with a lower effect size for the feeling of incomplete evacuation suggesting slightly less responsiveness to change over time.

In study OXN2401, the SEM for all patients at visit 3 was 9.01. In study OXN3401, a similar result was observed with an SEM of 7.59 and in study OXN3001 the SEM value was 8.16. These data would suggest that a patient may realize a clinically significant change in bowel function when a change of BFI score between 7.5 and 9 points is observed.

Similarly, across all studies the one-half SD for the total BFI score at visit 3 was observed to be 22.6 (study OXN2401), 25.3 (study OXN3401) and 23.3 (study OXN3001), so half SD ranges from 11.3 to 12.7. This value

suggests that changes in BFI total score of $≥12$ will be of clinical significance.

Discussion

The BFI has been developed to evaluate patient assessment of constipation. As a patient rating tool it has been used to evaluate the efficacy of prolonged release oxycodone combined with prolonged release naloxone. In a survey by Connell *et al* [36] 99% of the included patients ($n=1055$), which were defined as normal, non-constipated persons seen at health inspections in a factory and in patients seen at a general medical practitioner's surgery reported a stool frequency ranging from three times per week up to three times a day. This indicates that a diagnosis of constipation solely based on stool frequency may be misleading[37]. Many patients report a normal stool frequency but experience symptoms of constipation as straining, bloating and the feeling of incomplete bowel evacuation[2]. This makes clear that subjective measures need to be considered alongside objective measures like stool frequency and stool consistency[38,39].

The BFI was developed to take into account those subjective criteria often reported by patients who feel constipated. Since pain patients are experienced with the use of numerical rating scales to rate the intensity of their pain this kind of instrument was also used to develop the BFI. Three studies investigating the combination of PR oxycodone and PR naloxone in patients with moderate-to-severe chronic pain have been conducted to evaluate analgesia and impact on opioid-induced constipation[17,24–26]. In all studies
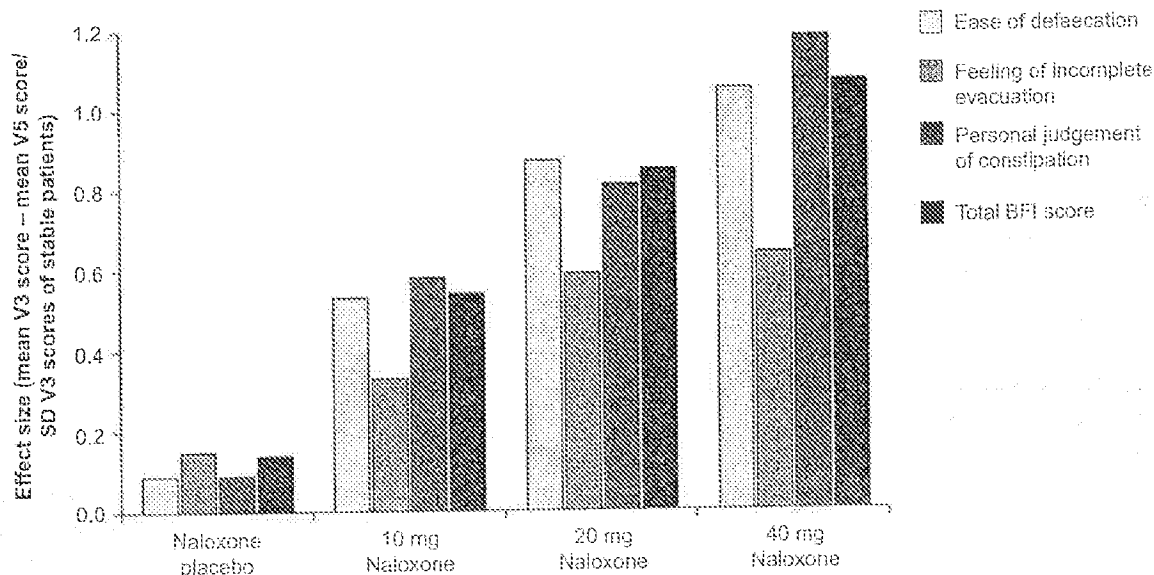

Figure 3a. Responsiveness of BFI in study OXN2401 (n =169). Responsiveness of individual BFI items and total BFI score by treatment group.
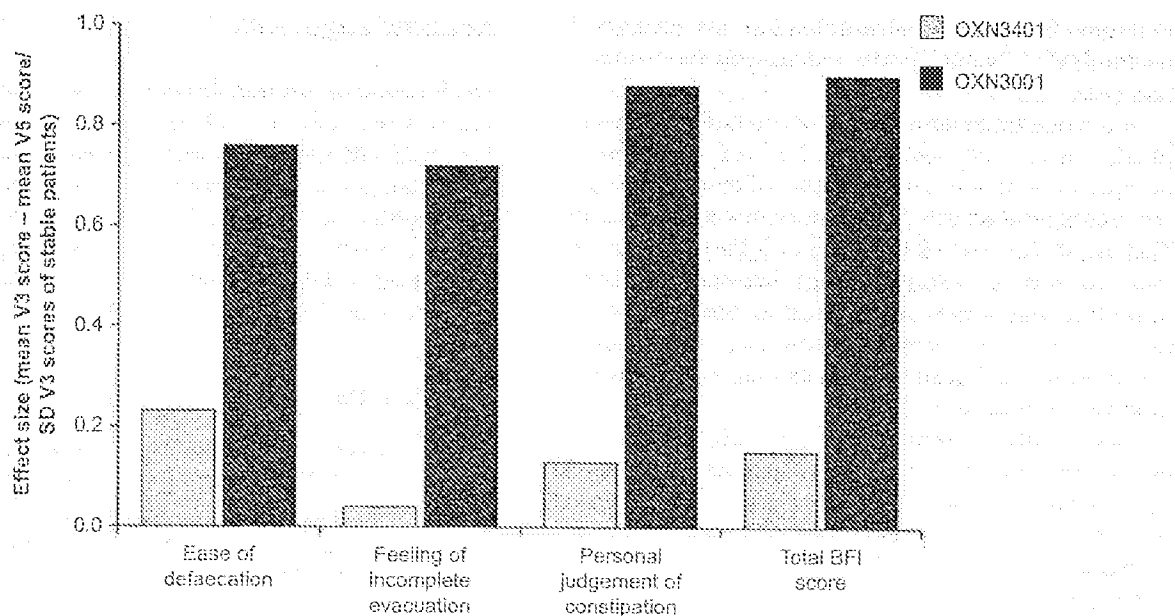
Figure 3b. Responsiveness of BFI in studies OXN3401 and OXN3001. Responsiveness of individual BFI items and total BFI score.

effective analgesia was undiminished by the presence of naloxone and an alleviation of constipation was observed. Data from these studies have been used to validate the BFI tool.

The level of missing data across the entire dataset was low (less than 0.5%), suggesting that the BFI tool is easy for patients to use and does not promote confusion or difficulty. The clinician administering the BFI is allowed to clarify the questions once per the BFI instruction sheet. By the end of the maintenance phase mean BFI scores were the lowest for all patients receiving active treatment (see also Figure 2). Not surprisingly, BFI scores were highest for those patients with more severe symptoms of constipation and clear significant differences between severe and mild constipation were observed. In one of the three studies, the BFI was not able to discriminate between those with mild and those with moderate constipation although in the other two studies, the BFI was able to discriminate between mild and moderate patients. These data indicate that the BFI tool can discriminate the severity of constipation based on stool consistency which can act as a surrogate marker for constipation severity *per se*.

There was strong internal consistency as measured by Cronbach's alpha for BFI total score and between individual BFI items. The observation of high internal consistency is indicative that each item of the BFI measure variables that are highly related. The highest correlations were observed between items of defecation and personal judgment. Similarly, the item to total score correlations were high, suggesting each item adds to the overall concept of the BFI. The lower correlation between BFI items of

defecation and personal judgment with feelings of incomplete evacuation is likely because this variable is distinct from the other two in the BFI tool and suggests that patients may judge feelings of constipation more on the ability to defecate rather than feelings of incomplete evacuation.

This evaluation study has shown that the BFI tool has good test-retest reliability and all correlations undertaken for reproducibility were in the moderate range for studies OXN2401 and OXN3401 and in the large range for study OXN3001. These data are supportive of the expectation that BFI scores will be stable during a period of time.

Patients who expressed a preference for PR oxycodone/ naloxone in the maintenance phases had better resolution of constipation symptoms than those expressing a preference during the titration phase. It would be anticipated that these patients were those for whom PR oxycodone/naloxone provided effective analgesia with an acceptable degree of side-effects. In study OXN3001, BFI correlated with the PAC-SYM suggesting that there is overlap between the BFI and PAC-SYM, but not outright redundancy with the stool and rectal scales of the PAC-SYM as these scales correlated more highly with the BFI than did the abdominal scale.

As expected when patients were grouped according to constipation severity, those with more severe symptoms demonstrated a higher BFI value suggesting that the BFI was valid in determining the impact of opioid-induced constipation. A systematic review of 83 studies has shown, that if patients with a chronic disease are asked to identify a minimal relevant change in health-related patient reported outcomes, the estimates fall very close to half a SD[14]. Therefore it can be concluded

that the threshold of discrimination for changes in health-related patient reported outcomes is approximately half a SD.

The remarkable consistency of the half SD criterion results across all studies made this criterion an accepted one in the determination of clinically important changes of health-related outcome measures. The FDA Draft Guidance for Industry on Patient Reported Outcome Measures states that for defining a minimum important difference, a distribution based approach (e.g., defining the minimal important difference as 0.5 times the SD) is acceptable as long as this result is not used in isolation[19].

Another distribution based approach, the standard error of measurement (SEM) for evaluating responsiveness was also taken into account, because it has been proposed as a useful statistic for evaluating clinically meaningful individual changes in health-related quality of life (HRQL) measures[34,35].

Analysis of the SEM and one-half SD characteristics of each BFI component indicated that changes in BFI score less than 7.5 points are unlikely to be clinically meaningful, whilst changes in BFI score of ≥12 points are likely to be related to clinically meaningful changes in patient's perception of their bowel habits. It is not known what the clinical relevance will be of BFI score changes between 7.5 and 12 points, score changes within this region would benefit from further evaluation. These values provide a guide to clinicians using the BFI tool with patients in aiding interpretation; however treatment in some patients may still provide a clinically meaningful effect at BFI changes less than 7.5 points[40].

Although this analysis includes a large sample of patients with OIC with measurements of stool frequency and consistency, and bowel function symptoms, the data are all from clinical trials whose primary focus was the evaluation of analgesic efficacy and bowel function regarding the fixed combination of oral PR oxycodone with oral PR naloxone. Further data for the validation of the BFI have been collected in a cross-sectional, observational, non-interventional, multicenter study in chronic, non-malignant pain patients receiving different opioid treatment. Results from this study will be discussed within another publication which is currently in preparation.

Taken together, the BFI is a valid and reliable instrument for the assessment of constipation evaluating the clinical symptoms in chronic pain patients. The findings of psychometric analyses from the phase II and phase III clinical trials support the BFI's psychometric properties, necessary information for interpretation of any data based on the BFI. Specific BFI score changes can be used for establishing thresholds for clinically meaningful change in constipation.

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