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OPIOIDS, SUBSTANCE ABUSE & ADDICTIONS SECTION

Review Article

Consensus Recommendations on Initiating Prescription Therapies for Opioid-Induced Constipation

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These consensus recommendations of the American Academy of Pain Medicine on initiating prescription therapies for opioid-induced constipation have been endorsed by the American Gastroenterological Association.

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Abstract

Objective. Aims of this consensus panel were to determine (1) an optimal symptom-based method for assessing opioid-induced constipation in clinical practice and (2) a threshold of symptom severity to prompt consideration of prescription therapy.

Methods. A multidisciplinary panel of 10 experts with extensive knowledge/experience with opioid-associated adverse events convened to discuss the literature on assessment methods used for opioid-induced constipation and reach consensus on each objective using the nominal group technique.

Results. Five validated assessment tools were evaluated: the Patient Assessment of Constipation–Symptoms (PAC-SYM), Patient Assessment of Constipation–Quality of Life (PAC-QOL), Stool Symptom Screener (SSS), Bowel Function Index (BFI), and Bowel Function Diary (BF-Diary). The 3-item BFI and 4-item SSS, both clinician administered, are the shortest tools. In published trials, the BFI and 12-item PAC-SYM are most commonly used. The 11-item BF-Diary is highly relevant in opioid-induced constipation and was developed and validated in accordance with US Food and Drug Administration guidelines. However, the panel believes that the complex scoring for this tool and the SSS, PAC-SYM, and 28-item PAC-QOL may be unfeasible for clinical practice. The BFI is psychometrically validated and responsive to changes in symptom severity; scores range from 0 to 100, with higher scores indicating greater severity and scores >28.8 points indicating constipation.

Conclusions. The BFI is a simple assessment tool with a validated threshold of clinically significant constipation. Prescription treatments for opioid-induced constipation should be considered for patients who have a BFI score of $\geq$30 points and an inadequate response to first-line interventions.

Key Words. Chronic Pain; Bowel Function Index; PAMORAs; Methylnaltrexone; Naloxegol; Lubiprostone

Introduction

Strategies for the management of pain commonly involve the use of opioid analgesics coupled with appropriate vigilance in patient selection and monitoring [1]. The analgesic efficacy of many opioids is attributable to actions exerted by these agents via μ-opioid receptors in the central nervous system [2]. Because μ-opioid receptors are also expressed throughout body tissues including the gastrointestinal tract [2], opioid analgesics are often associated with various types of opioid bowel dysfunction (OBD) [3,4]. Opioid-induced constipation (OIC) is the most prevalent OBD and is caused by opioid-mediated reductions in small intestinal and colonic transit, increased fluid absorption, inhibition of gastrointestinal chloride secretion, and stimulation or decreased relaxation of the pyloric and internal anal sphincters [4–7]. The condition has been reported in up to 47% of opioid-treated patients and may occur at a higher incidence in women and with increasing age; the greatest risk factor is a longer duration of opioid therapy [8]. Furthermore, OIC imposes a substantial burden on quality of life (QOL), reduces work productivity, impairs effectiveness of pain management, and can lead to clinically significant physical sequelae such as those related to bowel obstruction and fecal impaction [9,10].

Although the current Rome III diagnostic criteria provide a multifaceted definition of *functional constipation* [11], this condition is not opioid related, and a standardized OIC-focused definition is needed [12]. In 2014, a multidisciplinary consensus group proposed defining *OIC* as a change from baseline bowel habits upon initiation of opioids that is characterized by any of the following symptoms: (1) reduced bowel movement (BM) frequency; (2) development or worsening of straining to pass stool; (3) a sense of incomplete rectal evacuation; or (4) harder stool consistency [3]. In a 2015 systematic review, outcomes including BM frequency, stool consistency, straining, and QOL were suggested for use in OIC clinical trials [12]. However, the appropriateness of using these or other outcomes for assessing OIC in clinical practice has not been determined.

In view of the lack of a standardized definition for *OIC*, robust research guiding therapy for this condition is limited

[13]. To date, OIC has been predominantly managed with nonspecific laxative regimens [14,15]. Existing treatment standards for OIC suggest that opioid rotation, increased fluid and fiber intake, exercise, and over-the-counter (OTC) stool softeners, natural dietary supplements, and laxatives should be considered before evaluating a patient's need for prescription medications [16–19]. Most of these options are well-tolerated, readily available, and therefore recommended as first-line treatments; however, first-line agents are neither sufficiently supported by high-quality evidence nor associated with specific targeting of the opioid receptor–mediated mechanism of OIC [4,13,15]. Survey results have shown that only 46% of laxative-treated patients with OIC achieve their desired treatment outcomes frequently (i.e., >50% of the time) [15]. A 2013 systematic review concluded that large, well-designed studies of laxative efficacy in the treatment of OIC are needed [13].

Several prescription treatments used for OIC have been evaluated in large, multicenter, randomized, controlled trials. Despite the availability of these agents for the treatment of OIC, no guidelines published to date have provided a specific threshold for initiating pharmacologic prescription therapy. Two peripherally acting μ-opioid receptor antagonists (PAMORAs), methylnaltrexone (RELISTOR®; Salix Pharmaceuticals, Inc., Raleigh, NC, and Progenics Pharmaceuticals, Inc., Tarrytown, NY) and naloxegol (MOVANTIK™; AstraZeneca Pharmaceuticals LP, Wilmington, DE), are approved for the treatment of OIC [20,21]. Lubiprostone (AMITIZA®; Sucampo Pharma Americas, LLC, Bethesda, MD, and Takeda Pharmaceuticals America, Inc., Deerfield, IL) is a locally acting chloride channel activator that is also approved for the treatment of OIC, as well as for irritable bowel syndrome with constipation (IBS-C) in women and chronic idiopathic constipation (CIC) [22]. Although the high-affinity serotonin type-4 receptor agonist prucalopride (RESOLOR®; Shire Pharmaceuticals Ireland Ltd., Dublin, Ireland; Sanico NV, Turnhout, Belgium; and Janssen-Cilag SpA, Borgo San Michele, Italy) is not approved for OIC, this agent has been evaluated in OIC [23] and is approved in several countries (but not in the United States) for the treatment of chronic constipation [24,25]. Additional OIC-targeted prescription treatments are in development, including other PAMORAs and linaclotide (LINZESS®; Ironwood Pharmaceuticals, Inc., Cambridge, MA, and Actavis, Parsippany, NJ), a locally acting guanylate cyclase-C receptor agonist currently approved by the US Food and Drug Administration (FDA) for the treatment of CIC and IBS-C [3,26–29].

Appropriate selection of OIC prescription treatments may not be clear to prescribers because of the absence of guidelines or treatment algorithms that formally characterize patients who could benefit from these therapies. Thus, the purpose of this article is to present the views and recommendations of a multidisciplinary consensus panel regarding (1) the most effective method for assessing OIC and (2) the threshold in OIC symptom severity at which to consider initiation of OIC-targeted prescription medications in clinical practice.

Methods

On March 18, 2015, an OIC consensus panel meeting was held in Washington, DC. The panel comprised a multidisciplinary group of experts in pain, addiction medicine, neurology, palliative medicine, physiatry, anesthesiology, geriatrics, pharmacy, family practice, and gastroenterology. Prior to the meeting, panel members participated in a series of preparative conference calls and reviewed the literature on outcome measures and assessment tools used in OIC. Tools validated in OIC were identified by searching the PubMed database for articles published through 2014 using various combinations of the terms *opioid-induced constipation*, *opioids*, *constipation*, *instrument*, *assessment*, *tool*, *valid*, *validation*, *and validity*. Other measures and tools used (but not necessarily validated) in OIC trials were identified in a 2015 systematic literature review [12].

The nominal group technique [30,31] was used to reach consensus. This well-established and validated technique was selected on the basis of time availability and cost-effectiveness and to ensure the ability of all panel members to contribute to the final outcomes. The consensus meeting was standardized and followed several steps. First, a balanced review of the key literature identified prior to the meeting was presented by three panel members. During this presentation, three potential definitions were considered to help guide assessment method selection [3,11,12]. The 2014 definition for OIC proposed by Camilleri et al. [3] was selected on the basis of succinctness and the inclusion of both baseline bowel habits (i.e., BM frequency, straining, incomplete evacuation, and stool consistency) and a change in these habits upon initiation of opioid therapy. The presentation was followed by a description of the nominal group technique by the meeting facilitator.

During the remainder of the meeting, the panel addressed assessment methods followed by thresholds that may prompt consideration of prescription therapy in relation to each assessment method. Panel members independently completed worksheets to generate options based on the available evidence and practicality of application for each assessment method. Each panel member then shared his or her options, one at a time, while the facilitator recorded them on a computer screen projected to all participants. In a discussion session, the rationale for each option was elaborated on, supported, and/or defended. The panel then collectively produced a list of the most viable assessment options and recorded them on a priority sheet. Individual voting was completed by assigning a ranking to each option on the sheet, with higher rankings indicating greater importance. Voting outcomes were shared by the facilitator and further discussed by the group. Revisions and repeat voting were permitted but proved to be unnecessary.

Outcome Measures

Outcome measures may be either objectively measured or directly reported by patients. Objective outcome

measures can be collected by clinicians as well as by patients and typically provide numerical values for stool frequency, time-based outcomes (e.g., time to laxation, transit time [measured using the lactulose hydrogen breath test]), Bristol Stool Form Scale (BSFS) score (i.e., stool consistency) [12], and use of rescue therapy [23,32–36]. Patient-reported outcome (PRO) measures are direct reports from patients about how they feel or function with regard to a condition and its therapy, without interpretation by others [37]. In OIC, PROs include constipation intensity/severity, ease/difficulty of defecation, incomplete evacuation, straining, discomfort, constipation distress, and satisfaction (i.e., satisfaction with BMs or treatment) [12,35,38–45].

Objective Outcome Measures

The definition of OIC proposed by Camilleri et al. [3] includes two elements that are objectively measured—BM frequency and stool consistency, the latter commonly assessed using the BSFS [12,33]. Improvements in these outcomes have been identified as important to patients with OIC [9,18,46,47], and BM frequency is the central element used in most OIC clinical trials [12]. However, the degree of change in this outcome that is considered meaningful may vary among patients [18,47]. One longitudinal study found that patients with OIC would like to have $\geq$1 BM per day [18], whereas a separate study involving an online patient survey demonstrated that only 1 additional BM per week was viewed as a meaningful improvement [47]. Stool frequency and consistency are important to patients but may not sufficiently portray the severity of OIC [46,48] or the discomfort and other bothersome OIC symptoms [49].

Patient-Reported Outcome Measures

Compared with objective measures, PRO measures are more effective in capturing patient perceptions of constipation severity and patient experience [49]. The PROs of straining and incomplete rectal evacuation, both included in the proposed consensus definition of OIC [3], are common and highly bothersome among patients with the condition [9,46]. Other key PROs include pain/discomfort, bloating, fatigue, and fear or distress [9,44,47]. Many patients who experience these symptoms in the context of OIC would consider themselves constipated, regardless of stool frequency. However, there are no studies validating specific outcome measures. In addition, different scales are being used for the same outcome across trials (often inconsistently) [12]. Thus, in order to identify a comprehensive and practical method for assessing bowel function and determining changes in OIC severity, an analysis of formally validated PRO assessment tools is required.

Patient-Reported Outcome Assessment Tools

To identify patients with OIC in need of treatment, PRO assessment tools are commonly advocated [46]. The five PRO tools identified (Table 1) [3,12,46,48,50–58] each capture several PRO measures [59] and may also provide information on BM frequency [53,57]. Two Patient Assessment of Constipation (PAC) tools, the PAC-Symptoms (PAC-SYM) and the PAC-Quality of Life (PAC-QOL), were developed to address the need for standardized, constipation-specific PRO instruments [50,53,54,60]. The PAC-SYM stool symptoms domain was adapted by an expert advisory panel for pivotal OIC studies of naloxegol, which resulted in the shorter Stool Symptom Screener (SSS) [52,58]. Two PRO tools were developed specifically for OIC—the Bowel Function Diary (BF-Diary) [57] and the Bowel Function Index (BFI) (Figure 1) [48]. The BFI was designed for use in OIC studies to evaluate the effects of oxycodone prolonged-release (PR)/naloxone PR (TARGINIQ®; Purdue Pharma L.P., Stamford, CT) [49], an opioid agonist/antagonist combination for chronic pain [49,61].

Relevance in OIC

Items included in the five OIC assessment tools are somewhat varied. The BF-Diary includes items for assessing all four elements of the proposed OIC definition and a module to identify use of first-line interventions [3,57]. The PAC-SYM and SSS include items for assessing all but the BM frequency component of the proposed OIC definition [3,51,52]; the BFI and PAC-QOL each assess 1 component of the proposed definition—sense of incomplete rectal evacuation in the BFI and BM frequency in the PAC-QOL [46,54]. The BFI also includes two relatively general items, ease of defecation and personal judgment of the patient regarding constipation (Figure 1) [48], that may capture other OIC definition elements or key outcomes important in assessing OIC severity, such as bloating and pain [9,46,47,52]. These symptoms are also addressed by the BF-Diary and PAC tools [51,54,57].

Clinical Application

The clinical practicality of an assessment tool may be related to its length and ease of use and scoring. With only three items, the BFI is the shortest PRO assessment tool [46]. Each item is scored using a numerical analog scale from 0 to 100 points, which is similar to some scales used by patients with chronic pain in clinical trials [46,48,49]. Furthermore, clinicians can quickly assess OIC severity by calculating the total BFI index score using the average score of the three items [46]. Although the 4-item SSS is also relatively short, no information on calculating a total score is provided [52]. Similarly, the 3-module BF-Diary does not have a validated combined index score, and the 11 items (including two composite items) must be independently assessed [57]. Thus, this method was believed to be time-consuming, cumbersome, and inconvenient for most clinicians. The 12-item, 3-domain PAC-SYM [51,60] and the 28-item, 4-subscale PAC-QOL [54] have also been described as too cumbersome for use in a clinical setting [48].

Tool Administration

The PAC-SYM, PAC-QOL, and BF-Diary are self-administered by patients [50,53,57], whereas the BFI and SSS require that clinicians collect the PRO information

[48,52]. Involvement of the clinician may help to minimize inaccurate patient interpretations of instructions [46]. For self-administered tools, issues with a patient's reading or comprehension ability could result in failure to complete the assessment [46]. In contrast, patient administration limits the potential for clinician bias. Although the standardized BFI instructions (Figure 1) deter clinicians from leading the subjects in their answers [48], the risk of response bias may be inconsistent with the definition of a PRO, which specifies that the outcome should represent a report directly from the patient without interpretation by others [37]. Nevertheless, the clinician-administered BFI is practical in assessing OIC across a broad range of patients, including those with reading or comprehension challenges [44].

Recall Period

Recall periods for the five tools range from 1 to 14 days. For the PAC-SYM, the selection of a 14-day recall period was aimed at minimizing patient recall burden while ensuring sufficient time for a symptom complex characterized by relatively infrequent BMs [60]. During interviews on the SSS, 95.5% of patients reported they could remember their constipation symptoms "easily" or "very well" with a 14-day recall period [52]. However, authors of the validation article for the daily BF-Diary expressed concern that a 14-day recall period may be susceptible to error or bias [57]. The 7-day recall period for the BFI has been described as sufficiently short for appropriate recall but sufficiently long for ensuring clinical relevance with regard to BMs that may not occur on a daily basis [46].

Clinical Trials in OIC

The BFI and PAC-SYM are the most commonly used tools in published OIC clinical trials (Table 1). The BFI has been used as a primary or coprimary end point in seven published OIC trials reporting the efficacy and safety of oxycodone PR/naloxone PR [39,62–67]. The PAC-SYM has been used in five published OIC studies, including two studies of oxycodone PR/naloxone PR [39,64], one study of methylnaltrexone [68], one study of prucalopride [23], and one study of the μ-opioid receptor antagonist alvimopan (ENTEREG®; Cubist Pharmaceuticals U.S., Lexington, MA) [35,69]. The PAC-QOL was used in prucalopride, alvimopan, and methylnaltrexone studies [23,34,35]. The BF-Diary was used in a study designed to evaluate effects of the analgesic agent tapentadol IR (NUCYNTA®; Depomed Inc., Newark, CA), a combined μ-opioid receptor agonist and norepinephrine reuptake inhibitor, on bowel function and gastrointestinal tolerability [70,71]. All of these drugs showed significant improvements (relative to placebo or active comparators) [23,34,35,39,64,65,71], which supports the responsiveness of the assessment tools in patients receiving efficacious treatments for OIC.

Development and Validation of Assessment Tools in OIC

During deliberations, the OIC consensus panel considered 2009 FDA guidance on the development, documentation, and validation (i.e., content and construct validity) of PRO assessment tools [59]. In the literature, the BFI has been validated in OIC most frequently, with three publications collectively showing reliability and internal consistency, convergent and known-groups validity, and a clinically meaningful BFI score change of $\geq$12 points [48,55,56]. The validation program also confirmed the ability of BFI values from 27 to 29 points to differentiate patients with constipation from those without constipation [55]. These scores support previous findings by Ueberall et al. [49] that defined a reference range of BFI scores reflecting nonconstipation in chronic pain; this range had a 28.8-point upper limit and included 95% of the nonconstipated population (Figure 2). However, content validation of the BFI has not been documented. For the BF-Diary, a single validation publication has documented both content and construct validity [57], consistent with FDA guidelines [59]. The PAC-SYM has shown concurrent validity in patients with OIC [51], and the SSS has shown adequate content validity [52]. No content or construct validation articles in OIC have been published for the PAC-QOL.

Discussion and Recommendations

Initial Clinical Considerations Related to Diagnosis and Prophylactic and First-Line Interventions

Although this consensus article is not intended to provide specific treatment recommendations, we highlight the need to consider selected factors before evaluating whether treatment with OIC prescription medication is warranted. In anticipation of potential OIC development with long-term opioid use, treatment guidelines recommend initiation of a prophylactic bowel regimen that may involve increased fluid and fiber intake, stool softeners, and/or laxatives [16,17,72]. When a diagnosis of OIC is suspected despite prophylactic treatment, clinicians should confirm that initiation of opioid therapy has led to a change from baseline in the patient's typical bowel habits, as defined by Camilleri et al. [3], before consideration of further or alternative interventions. First-line approaches to intervention also include dietary changes and OTC treatments as well as exercise [16,17]. However, prophylactic and first-line OTC therapies for OIC may not consistently and predictably lead to desired treatment responses [15,46], and the number and quality of OIC studies of such therapies are inadequate to determine their efficacy and tolerability [13]. Nevertheless, the panel believes that the accessibility and relatively low risk of dietary and OTC options justify their prophylactic and first-line use for OIC.

Enemas/rectal suppositories and manual evacuation, which are sometimes recommended for patients with constipation [72], are associated with invasiveness,

Table 1 PRO assessment tools

Tool	Length	Symptoms/Outcomes Evaluated*	Scores			Administration	Recall Period	No. of OIC Clinical Trial Publications [12]	No. of OIC Validation Publications	
			Items	Subscores	Total				Content Validity	Construct Validity
PAC-SYM [50,51]	12 items (3 domains)	I. Abdominal (i.e., discomfort, pain, bloating, cramping) II. Rectal (i.e., pain, burning, bleeding/tearing) III. Stool (i.e., **incomplete BMs**, **consistency**, size, **straining**, inability to defecate/false alarm)	0–4	Average of items 1–4; 5–7; and 8–12	Average of all 12 items	Patient administered	14 days	5†	0	1
SSS [52]	4 items	Four of the 5 items from the PAC-SYM stool symptoms domain: I. **Incomplete BMs** II. **Stool consistency** III. **Straining** IV. Inability to defecate/false alarm	0–4	N/A	N/A	Clinician administered	14 days	0‡	1	0
PAC-QOL [53,54]	28 items (4 subscales)	I. Physical discomfort (e.g., bloating) II. Psychosocial discomfort (e.g., embarrassment, decreased appetite) III. Worries and concerns (e.g., anxiety, fear) IV. Satisfaction (e.g., **with BM frequency**)	0–4	Average of items 1–4; 5–12; 13–23; and 24–28	Average of all 28 items	Patient administered	14 days	3	0	0

Table 1 *Continued*

Tool	Length	Symptoms/Outcomes Evaluated*	Scores			Administration	Recall Period	No. of OIC Clinical Trial Publications [12]	No. of OIC Validation Publications	
			Items	Subscores	Total				Content Validity	Construct Validity
BFI [46,48,55,56]	3 items	I. Ease of defecation II. **Incomplete evacuation** III. Patients' judgment of constipation	0 to 100	N/A	Average of all 3 items	Clinician administered	7 days	7	0	3
BF-Diary [57]	11 items[§] (3 modules)	I. BM assessment (e.g., **straining, incomplete evacuation**, rectal pain, **stool consistency**) II. Daily/symptom assessment (e.g., inability to defecate, bloating, abdominal pain, bothersome gas, lack of appetite) III. Treatments used (e.g., fiber, laxatives) Composite items: **SBMs/wk, SCBMs/wk**	Varies by item	N/A	N/A	Patient administered	After each BM and daily	1	1	1

Abbreviations: BF-Diary, Bowel Function Diary; BFI, Bowel Function Index; BM, bowel movement; N/A, not applicable; OIC, opioid-induced constipation; PAC-QOL, Patient Assessment of Constipation–Quality of Life; PAC-SYM, Patient Assessment of Constipation–Symptoms; SBM, spontaneous bowel movement; SCBM, spontaneous complete bowel movement; SSS, Stool Symptom Screener.

* Symptoms/outcomes included in the proposed OIC definition [3] are in bold.

† One additional OIC clinical trial publication used the sum score of rectal and stool symptom domains of the PAC-SYM.

‡ Although the primary publication for the SSS indicates that this tool was adapted from the PAC-SYM for use in the naloxegol clinical program, published phase 3 naloxegol studies do not include any details on the use or results of this tool [52,58].

§ Includes two composite items.

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 patient's 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 difficulty 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 1 The BFI assessment tool and instructions for use. Abbreviation: BFI, Bowel Function Index. Reproduced with permission from: Rentz AM, Yu R, Müller-Lissner S, Leyendecker P. Validation of the Bowel Function Index to detect clinically meaningful changes in opioid-induced constipation. J Med Econ 2009;12:371–83. Copyright 2009 Informa Healthcare.

discomfort, embarrassment, and health care burdens. Rectal procedures have been described as painful and traumatic for patients and may lead to complications such as rectal bleeding or bowel perforation, especially in patients who have thrombocytopenia or are receiving anticoagulation therapy [19,73,74]. For manual evacuation, competent practitioners should be involved in cautious execution and only when absolutely necessary [19,73,75,76] after OTC and prescription therapies have been exhausted. Particular caution is required to avoid invasive options in patients who are immunocompromised because of the risk of producing a systemic infection [19,73,75]. The health care burden and costs of enemas and manual evacuation are reflected in results from a palliative care study showing that the total health care staff time spent on these processes was

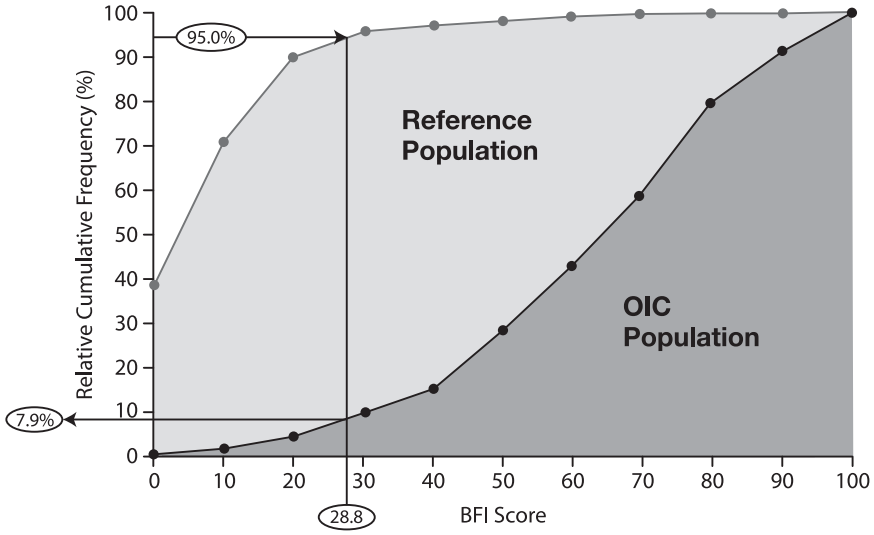

Figure 2 Relative cumulative frequencies of BFI scores for the reference and OIC populations. The reference population comprised nonconstipated patients with chronic pain who were treated with WHO step I and II analgesics; the OIC population comprised patients with chronic pain who had been pretreated with WHO step III opioids and laxative regimens and who reported constipation caused or aggravated by an opioid; 95% of the reference population and 7.9% of the OIC population had a BFI score $\leq$28.8 points. Abbreviations: BFI, Bowel Function Index; OIC, opioid-induced constipation; WHO, World Health Organization. Adapted with permission from: Ueberall MA, Müller-Lissner S, Buschmann-Kramm C, Bosse B. The Bowel Function Index for evaluating constipation in pain patients: definition of a reference range for a nonconstipated population of pain patients. J Int Med Res 2011;39:41–50. Copyright 2011 SAGE Publications.

higher than time spent on most other tasks related to the management of constipation (e.g., oral laxative administration, discussions of bowel care) [76].

The panel maintains that initial consideration of first-line OTC interventions for OIC is essential because these approaches may be effective for some patients; however, failure of these options to provide adequate relief should be determined quickly to facilitate consideration of further intervention with PAMORAs (i.e., methylnaltrexone and naloxegol) or other newer prescription medications (e.g., lubiprostone), consistent with the literature [72].

The Panel Recommends the Bowel Function Index for Assessing OIC

To ensure rapid and reliable assessment of OIC by clinicians, a simple and easy-to-use method was preferred by the panel. Practicality is critical in selecting a validated assessment tool for universal application across clinical settings. The BFI is a simple, clinically responsive, and validated tool with a clear published threshold for constipation [49,55]. On the basis of the panel members' clinical experience, patients with OIC rarely feel satisfied with the completeness of their BM evacuations, thereby supporting the relevance of the second BFI item (i.e., incomplete evacuation) to OIC. The other two items (i.e., ease of defecation, personal judgment of constipation) are general but may indirectly provide insight into information that is important to each patient (e.g., straining, changes in BM frequency, abdominal symptoms). Perceptions of these general and subjective items may vary among patients. Significant correlations demonstrated between the BFI and both the PAC-SYM and PAC-QOL [55,56] provide reassurance that the BFI captures the symptoms relevant in OIC. Although shorter recall periods are generally preferred for PRO assessments, the 7-day recall period of the BFI may be appropriate given the general nature of its items. The requirement for a clinician to administer the BFI is acceptable but may represent a limitation of this PRO assessment tool.

Other options proposed by the panel, which would require formal validation, involved use of the BFI in combination with BM frequency or a BF-Diary module. Stool frequency is perceived as highly important to patients [18,47], is included in the proposed OIC definition [3], and can be easily tracked in OIC trials. However, in clinical practice, some patients may have difficulty in accurately recalling this outcome. With regard to BF-Diary modules, which capture OIC definition elements [3] and the use of other interventions, index scoring has not been validated [57]. The panel concluded that the complexity involved in individually assessing each BF-Diary item in a module might be too cumbersome for universal clinical application.

The Panel Recommends a Score of $\geq$30 Points on the Bowel Function Index for Consideration of Prescription Medications in Patients With Previous or Current Use of First-line Interventions

A score of $\geq$30 points on the BFI was ultimately selected on the basis of a study conducted by Ueberall

et al. [49] that identified a reference range of 0–28.8 points for most (i.e., 95%) nonconstipated patients with chronic pain. The selected threshold was also based on the general belief that patients should not be denied consideration for further therapy if they surpass the range of nonconstipation, provided that they have also shown inadequate responses to first-line options. The panel recommends rounding the upper 95% limit of the nonconstipated range on the BFI (i.e., 28.8 points) to 30 points in order to provide a simpler, slightly more conservative, and memorable minimum threshold for application in clinical settings. This threshold includes the scores documented for approximately 90% of the OIC cohort evaluated by Ueberall et al. (Figure 2) [49]. This OIC cohort is relevant, as it was derived from a pooled analysis of two studies in which patients, most of whom had been pretreated with World Health Organization step III opioids and laxative regimens, reported constipation (i.e., <3 complete spontaneous BMs per week, without the need to strain) that was caused or aggravated by an opioid [49,77]. Thus, the panel determined that the selected threshold is generalizable to the overall OIC population.

Higher cutoffs of ≥40 or ≥50 points represent values that incorporate both the upper 95% limit of the nonconstipated range defined by Ueberall et al. [49] (i.e., ≤28.8 points) and a clinically meaningful increase of ≥12 points identified by Rentz et al. [48]. However, for theoretical cutoff scores, higher magnitudes of increase beyond 28.8 points would result in the exclusion of higher percentages of patients who could otherwise benefit from prescription therapy (Figure 2) [49]. For example, a ≥50-point theoretical threshold would include approximately 70% of the OIC cohort in the Ueberall et al. study but would also exclude up to 30% of these OIC patients from potentially receiving further interventions (Figure 2) [49].

Supplementary Assessments for OIC

The panel recognizes that the BFI may be insufficient in some clinical settings. As such, the BFI may be supplemented with additional outcome measures as necessary on the basis of clinical judgment and individual patient needs. Changes from baseline in BM frequency may be relevant for patients who are able to accurately recall this information. The BSFS may be helpful as a patient education tool and in patients who require a visual method of communication, such as those with cognitive impairment, advanced or serious illness, or other challenges including verbal difficulties and low literacy level.

Proposed Future Efforts in the Assessment of OIC

The panel acknowledges that the BFI may not precisely capture the symptoms and outcomes relevant in OIC. Therefore, development and validation of additional assessment tools for OIC that have comparable or better practicality and ease of use are warranted. For optimal efficiency, future tools might comprise a single question that incorporates the most important aspects of OIC (e.g., "While on opioid therapy, do you have painful or difficult BMs that have not been relieved by laxatives?"). A tool that has the flexibility to be either patient or clinician administered may minimize the potential for clinician bias while maintaining the option, if needed, to avoid patient miscommunication or misinterpretation. Additional clinical studies are needed to help improve understanding of baseline bowel habits and the effectiveness of OTC therapies in OIC.

Conclusions

OIC is common in patients with chronic pain who are receiving opioid therapy, and the condition may have a substantial impact on QOL. The BFI is a practical, validated, and responsive assessment tool that is clinically relevant in OIC. After prophylactic and first-line interventions have been evaluated, a BFI score of ≥30 points should prompt consideration of prescription OIC medications such as currently available PAMORAs (i.e., methylnaltrexone and naloxegol) or lubiprostone. If necessary, BFI results may be supplemented with assessments that are appropriate on the basis of the clinical setting and individual patient needs, as judged by the clinician. Development and validation of additional OIC assessment tools are warranted.

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