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Patient Assessment of Constipation Quality of Life Questionnaire: Validation in Greek patients under medication for addiction treatment with methadone and buprenorphine

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Research Article

Keywords: constipation, methadone, buprenorphine, quality of life, validation, opioid addiction

Posted Date: March 11th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9082896/v1

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Additional Declarations: The authors declare no competing interests.

Abstract

Methadone maintenance treatment (MMT) and buprenorphine maintenance treatment (BMT) are considered effective for opioid use disorders. However, they have been associated with side-effects in the gastrointestinal system, mainly opioid-induced constipation that impairs patient quality of life (QoL). This investigation aimed to validate the patient assessment of constipation quality of life (PAC-QoL) instrument in Greek patients under medication for addiction treatment (MAT) by examining reliability and construct validity. In total, 310 patients under MAT were included in the investigation and completed PAC-QoL questionnaire, Nottingham health profile (NHP) instrument and Bristol stool form scale (BSFS) in Phases 1 (baseline) and 2 (12 days post baseline).The content validity was evaluated by using the item content validity index (I-CVI) along with ceiling and floor effects, internal consistency by measuring Cronbach's a coefficient, test-retest reliability through intraclass correlation coefficient (ICC), responsiveness with effect size estimation, and convergent validity by correlations with NHP and BSFS. According to the results, a strong positive correlation among PAC-QoL sub-scales was observed. The overall ICC was equal to 0.90, the I-CVI was equal to 1.00, and the Cronbach's alpha was estimated to the value of 0.96. Furthermore, it appears that the MMT patients experience more severe constipation than their BMT counterparts, and effect size for the total instrument was 0.94. The findings suggest an excellent reliability and validity of PAC-QoL in the Greek language. Moreover, its implementation in research and clinical settings is advocated as a useful tool to identify constipation related to QoL in patients under MAT.

Introduction

Methadone maintenance treatment (MMT) and buprenorphine maintenance treatment (BMT) are considered the most effective medications for addiction treatment (MAT) for patients with opioid use disorders (OUDs). As such, they lead to the reduction of craving for illicit opioids, and to the attenuation of severe side-effects of OUDs to human health. Therefore, they contribute to the decrease of communicable disease transmission, and to the amelioration of drug seeking behavior (Reed et al., 2023). In the biochemical level, methadone binds to mu-opioid receptors (MORs) as a full agonist and activates also the kappa (k) opioid receptors (KORs) and delta (d) opioid receptors (DORs). On the contrary, buprenorphine acts as a partial agonist of MORs and a full antagonist of KORs (Leventelis et al., 2019). Both substances, when they are used as MAT, exert beneficial effects on several health parameters of the addicted patients. However, they have also been associated with biochemical side-effects such as neuroinflammation and oxidative stress (Leventelis et al., 2019, 2025a). Moreover, they appear to induce sexual malfunctions, insomnia, and serious complications of the gastrointestinal system such as defective swallowing, dry mouth and constipation. Overall, they adversely influence retention to opioid-assisted treatment and to the quality of life (QoL) of the addicted patients (Haber et al., 2017; Leventelis et al., 2019, 2025a).

Constipation constitutes a serious defecation symptom that is related to nutritional deficits, sedentary lifestyle and irritable bowel. It is characterized by infrequent stool generation and difficulties in stool

passage (Bellini et al., 2021; Sason et al., 2021). According to Rome IV criteria, constipation is categorized into the following four subtypes: functional constipation (FC), irritable bowel syndrome with constipation (IBS-C), functional defecation disorders, and opioid-induced constipation (OIC). The diagnostic criteria of OIC are similar to those of FC including hard stools, and a sensation of incomplete evacuation in at least 25% of defecations, less than three bowel movements per week, and use of manual means for removing stools from the rectum with the requisite that new or older symptoms occur due to opioid use (Aziz et al., 2020; Sizar et al., 2023). The incidence of OIC varies from 40% to 60% of patients receiving opioids without suffering from cancer (Kandhi et al., 2022). This involves the activation of opioid receptors, especially MORs, which are widely distributed throughout the gastrointestinal tract producing decreased faecal volume that leads to negative effect of gut motility resulting in harder, drier faeces and straining difficulties (Farmer et al., 2019; Sason et al., 2021). The prevalence of constipation induced by both methadone and buprenorphine as MAT is met in > 60% of patients and is accompanied by excessive sweating, dehydration, and fatigue, symptoms that highly affect QoL and retention to treatment (Haber et al., 2017; Lugoboni et al., 2016). Furthermore, OIC in patients under MAT is related to pre-existed psychological factors, personality features, mood and anxiety disorders and plays a pivotal role in the efficacy of medication (Khangura & Ryce, 2021; Peckham et al., 2020; Samokhvalov & Rehm, 2015)

Although OIC is a common and frequent side-effect of MAT, it is an under-recognized, underdiagnosed, undertreated and rather neglected symptom of patients with OUDs (Lugoboni et al., 2016). Moreover, due to the limited number of validated instruments for the assessment of constipation in those patients, there is scarce evidence regarding the severe impact of this unpleasant and pathological condition on addiction treatment. Thus, the aim of the present investigation was to assess the reliability and validity of the patient assessment of constipation quality of life (PAC-QoL) scale in patients under MAT with methadone and buprenorphine.

Material and methods

Participants and procedure

According to the literature, the recommended number of participants for the validation of a questionnaire must be typically equal to 10 times the number of the items of the instrument (DeVellis, 2017). PAC-QoL instrument consists of 28 items, and considering a 10% dropout, 308 patients were considered as an adequate number for the validation of the questionnaire. The randomization process using electronic software, which was based on the patient unique code before MAT programs admission, was performed by an independent individual, who did not participate in the data collection and evaluation procedure. This individual had access to interim results and was responsible for terminating the procedure in case there was a need for that, or any adverse effect had been raised before addressed to the appropriate expert. A total of 310 patients under MAT were divided, according to their medication, namely methadone or buprenorphine, into two groups, MMT (n = 164) and BMT (n = 146). All participants completed the PAC-QoL instrument, the Bristol stool form scale (BSFS) for the evaluation of the form of

fecal content, and the Nottingham health profile (NHP) for the assessment of patient QoL in two different periods, namely phase 1 (baseline) and phase 2 (12 days post baseline), to assess the test-retest reliability of PAC-QoL questionnaire. As it has been shown, the time interval between measurements may influence the interpretation of the reliability in the test-retest procedure, thus, a time period between 10 and 14 days is considered adequate for this process (Souza et al., 2017).

All patients were fully informed about the purpose and objectives of the investigation. The confidentiality of personal data was completely ensured, and each patient signed a consensus form for participation in the study and data publication before study begun. According to the inclusion criteria, the patients should be over 20 years old, long-term users of opioid substances suffering from physical and mental dependence, and they should be active members in MAT programs. Patients with severe psychopathology and serious pathological problems, which impaired attending the experimental procedure, were excluded from the study. Moreover, demographic information of the volunteers regarding gender, age, educational level, nationality, social status, place of residence, area, duration of MAT program attendance, age of onset and duration of using addictive substances before entering MAT programs was also collected.

Description of the instruments

The Patient assessment of constipation quality of life instrument (PAC-QoL)

PAC-QoL is consisted of 28 self-reported items that assess the effects of constipation on QoL during the last 2 weeks. It is divided into four sub-scales: worries/concern (11 items), physical discomfort (4 items), psychosocial discomfort (8 items), and satisfaction (5 items). The responses are scored on a Likert scale ranging from 0 to 4, wherein higher score represents poorer QoL (Marquis et al., 2005). The original English version of PAC-QoL scale (Copyright©PAC-QOL, 2005 Mapi Research Trust, all rights reserved), that was developed and initially validated by Marquis et al. (2005), was translated into the present Greek language and then translated in English by a different translator. After that, both original and back-translated PAC-QoL were compared, and the discrepancies were resolved by a third bilingual translator who was not involved in the previous translations to accurately reflect the intent-accuracy of the item wording. The readability of the instrument was reviewed by a native Greek linguist. Then, 50 patients were invited to assess the translated questionnaire for language clarity and items readability and to identify potential difficulties in its completion.

Bristol stool form scale (BSFS)

BSFS is a graphical representation of each stool type for the evaluation of the form of fecal content ranging from the hardest (Type 1) to the softest (Type 7) according to its shape and consistency related to specific bowel symptoms. Type 1 (separate hard lumps) and Type 2 (sausage shape but lumpy) are related to the severity of constipation (Chumpitazi et al., 2016; Martinez & de Azevedo, 2012).

Nottingham health profile (NHP)

NHP is a self-reported instrument for the evaluation of QoL in patients under MAT. It assesses the discomfort of an individual that suffers from various health problems and their effects on his/her everyday activities. The validity and reliability were high as they were assessed with test-retest reliability coefficient, since Spearman's r-value ranged between 0.77 and 0.86 (Leventelis et al., 2020).

MAT administration

The patients were under either methadone hydrochloride solution (10 mg/ml), buprenorphine or buprenorphine/naloxone tablets (2–8 mg). Mean doses of methadone and buprenorphine were equal to 89.8 mg/24 h and 12.0 mg/24 h, respectively. According to the literature, daily doses of methadone between 40 mg – 100 mg and buprenorphine between 12 mg – 14 mg are considered effective (Saxon et al., 2013; Strain et al., 1999).

Ethical considerations

This study was performed in line with the European Union guidelines under the 1975 Helsinki Declaration as revised in 2013 and was approved from the Institutional Review Board of the XXX Organization (ref. number XXX). A written informed consent for participation in the study and data publication was provided by all volunteers before the start of the experimental procedure.

Statistical analysis

Quantitative variables were expressed as mean values ± standard deviation (SD), and qualitative variables were expressed as absolute and relative frequencies. Student's t-test was used to determine whether there is a significant difference between the mean values examined in the two groups. Internal consistency reliability was determined by the calculation of Cronbach's α coefficient. Scales with reliabilities equal to or greater than 0.70 were considered acceptable. The Pearson correlation coefficient was calculated to assess the relationships among various factors of the PAC-QoL questionnaire, including physical discomfort, psychological discomfort, worries and discomfort, treatment satisfaction, and the total score. The resulting coefficients provide insight into how these factors are related with higher values indicating stronger associations between the factors under consideration. The intraclass correlation coefficient (ICC) between the scores for phases 1 and 2 was calculated separately for each PAC-QoL subscale and the total score was evaluated using the Pingouin statistical package in Python (Vallat, 2018). The data was reshaped into long format and analyzed using a two-way mixed-effects model (absolute agreement), suitable for evaluating test-retest reliability.

Content validity was examined by a panel of 10 experts in the fields of medical pathology, psychiatry, nursing, psychology, biochemistry and biostatistics which was formed to finally assure that the two questionnaire versions were closely equivalent. Each expert rated every item on a scale from 1 to 4 (1 = not related, 2 = partly linked, 3 = closely related, and 4 = completely related), and an item content validity

index (I-CVI) was then computed using the formula: I-CVI = (Number of experts who rated the item as "relevant") / (Total number of experts). An I-CVI ≥ 0.8 is considered acceptable (Zamanzadeh et al., 2015). Ceiling and floor effects were assessed to evaluate the extent to which participants clustered at the upper or lower extremes of the PAC-QoL scale. A ceiling effect occurs when a large proportion of respondents achieve the maximum score, suggesting limited ability of the instrument to detect improvement. A floor effect refers to a high concentration of minimum scores, potentially masking deterioration. Conventionally, a threshold of 15% is used, where effects are considered present if more than 15% of responses fall at either extreme (Terwee et al., 2007).

In regards to construct validity, the suitability of the dataset was assessed by measuring the Kaiser-Meyer-Olkin (KMO) and Bartlett's index. A Confirmatory Factor Analysis (CFA) was carried out to test the validity of the four sub-scale structure using the Comparative Fit Index (CFI), the Tucker-Lewis Index (TLI) and the Root Mean Square Error of Approximation (RMSEA) (Hu & Bentler, 1999). For the CFI and TLI indices, it is considered that values close to or greater than 0.95 reflect a good fit to the data (Hu & Bentler, 1999). RMSEA values that are less than 0.06 indicate a good fit and values as high as 0.08 indicate a reasonable fit (Kim et al., 2016). Convergent validity was assessed through the correlation of PAC-QoL with the BSFS and the NHP using Pearson’s correlational analysis (r). The effect size was calculated using Cohen's d test that quantifies the magnitude of the difference between two group means in terms of their pooled standard deviation. This measure provides crucial insight into the practical significance of a finding, with conventional interpretations classifying d values of 0.2, 0.5, and 0.8 as representing small, medium, and large effect sizes, respectively. Reporting this effect size allows for a more complete understanding of how substantially the groups differ between each another. Discriminant construct validity was evaluated by comparing PAC-QoL impact questionnaire sub-scales and the total between the two substances using Student’s t-test. All reported p values were two-tailed. The statistical significance threshold was set at 0.05, and the data analysis was performed using Python and R software.

Results

The demographic characteristics of the participants are presented in Table 1. The majority of the volunteers were male in both groups, they were single and residents of urban areas. The mean ages of MMT and BMT participants were 47.0 years old (± 7.1) and 45.9 years (± 6.8) respectively, and mean age of first use for MMT and BMT was 17.7 ± 5.3 years and 22.9 ± 7.6 years respectively.

Table 1
The demographic characteristics of the participants.

Demographic data		**MMT**	**BMT**
		N (%)	**N (%)**
Gender	Female	69 (42.1)	30 (20.5)
	Male	95 (57.9)	116 (79.5)
Education level	Illiterate	0 (0.0)	0 (0.0)
	Primary school	34 (20.7)	51 (34.9)
	Secondary school	62 (37.8)	25 (17.1)
	Under/Postgraduate	68 (41.5)	70 (48.0)
Family status	Married	46 (28.0)	55 (37.6)
	Single	76 (46.3)	70 (48.0)
	Widowed	0 (0.0)	5 (3.4)
	Divorced/Separated	42 (25.7])	16 (11.0)
Work status	Employed	116 (70.7)	112 (76.7)
	Unemployed	48 (29.3)	34 (23.3)
Place of residence	Urban	133 (81.1)	79 (54.1)
	Rural	31 (18.9)	67 (45.9)
		MMT	**BMT**
		Mean (± SD)	**Mean (± SD)**
	Age	47.0 (± 7.1)	45.9 (± 6.8)
	Age of onset of drug use	17.7 (± 5.3)	22.9 (± 7.6)
	Years of drug use prior MAT	13.7 (± 8.1)	16.2 (± 8.7)
	Years in MAT program	13.2 (± 5.8)	8.6 (± 3.7)
	Dose	89.8 (± 22.6)	12.0 (± 4.0)

MMT: Methadone maintenance treatment; BMT: Buprenorphine maintenance treatment; MAT: Medication for addiction treatment; SD: Standard deviation

(Insert Table 1 here)

The questions of the PAC-QoL, as answered by the participants, are presented in Table 2.

Table 2
The items of PAC-QoL

The following questions are related to symptoms of constipation. During the past two weeks, to what extent or intensity...		**Not at all (0)**	**A little bit (1)**	**Moderately (2)**	**Quite a bit (3)**	**Extremely (4)**
		n (%)				
Q1	have you felt bloated to the point of bursting?	0 (0.0)	14 (4.5)	146 (47.1)	143 (46.1)	7 (2.3)
Q2	have you felt heavy because of your constipation?	3 (0.9)	13 (4.2)	140 (45.2)	154 (49.7)	0 (0.0)
The following questions are related to constipation and daily life. How much time in the past two weeks...		**None of the time (0)**	**A little of the time (1)**	**Some of the time (2)**	**Most of the time (3)**	**All of the time (4)**
		n (%)				
Q3	have you felt any physical discomfort?	4 (1.3)	10 (3.2)	162 (52.3)	134 (43.2)	0 (0.0)
Q4	have you felt the need to open your bowel but not been able to?	5 (1.6)	20 (6.4)	156 (50.3)	129 (41.7)	0 (0.0)
Q5	have you been embarrassed to be with other people?	5 (1.6)	15 (4.8)	151 (48.7)	139 (44.9)	0 (0.0)
Q6	have you been eating less and less because of not being able to have bowel movements?	5 (1.6)	9 (2.9)	152 (49.0)	144 (46.5)	0 (0.0)
The next questions assess the effects of constipation on your daily life. To what extent, during the past 2 weeks...		**Not at all (0)**	**A little bit (1)**	**Moderately (2)**	**Quite a bit (3)**	**Extremely (4)**
		n (%)				
Q7	have you had to be careful about what you eat?	4 (1.3)	12 (3.9)	131 (42.2)	163 (52.6)	0 (0.0)
Q8	have you had a decreased appetite?	5 (1.6)	5 (1.6)	136 (43.9)	164 (52.9)	0 (0.0)
Q9	have you been worried about not being able to choose what you eat (for example, at a friend's place)?	5 (1.6)	12 (3.9)	155 (50.0)	138 (44.5)	0 (0.0)

The following questions are related to symptoms of constipation. During the past two weeks, to what extent or intensity...		Not at all (0)	A little bit (1)	Moderately (2)	Quite a bit (3)	Extremely (4)
		n (%)				
Q10	have you been embarrassed about staying in the toilet for a long time when you were away from home?	6 (1.9)	14 (4.5)	151 (48.7)	139 (44.9)	0 (0.0)
Q11	have you been embarrassed about having to go to the toilet very often when you were away from home?	7 (2.3)	13 (4.2)	131 (42.2)	159 (51.3)	0 (0.0)
Q12	have you been worried about having to change your daily routine (for example, travelling, being away from home)?	6 (1.9)	4 (1.3)	141 (45.5)	159 (51.3)	0 (0.0)
The next few questions assess your feelings. How much of the time, during the past 2 weeks…		**None of the time (0)**	**A little of the time (1)**	**Some of the time (2)**	**Most of the time (3)**	**All of the time (4)**
		n (%)				
Q13	have you felt irritable because of your condition?	4 (1.3)	23 (7.4)	125 (40.3)	158 (51.0)	0 (0.0)
Q14	have you been upset because of your condition?	5 (1.6)	8 (2.5)	139 (44.9)	153 (49.4)	5 (1.6)
Q15	have you felt obsessed because of your condition?	6 (1.9)	11 (3.5)	160 (51.7)	133 (42.9)	0 (0.0)
Q16	have you felt stressed because of your condition?	8 (2.6)	3 (0.9)	145 (46.8)	149 (48.1)	5 (1.6)
Q17	have you been less self-confident because of your condition?	8 (2.6)	8 (2.6)	151 (48.7)	135 (43.5)	8 (2.6)
Q18	have you felt in control of your situation?	4 (1.3)	25 (8.0)	145 (46.8)	128 (41.3)	8 (2.6)
The next questions assess your feelings. To what extent, during the past 2 weeks...		**Not at all (0)**	**A little bit (1)**	**Moderately (2)**	**Quite a bit (3)**	**Extremely (4)**
		n (%)				

The following questions are related to symptoms of constipation. During the past two weeks, to what extent or intensity...		Not at all (0)	A little bit (1)	Moderately (2)	Quite a bit (3)	Extremely (4)
		n (%)				
Q19	have you been worried about not knowing when you are going to be able to have a bowel movement?	1 (0.3)	12 (3.9)	156 (50.3)	137 (44.2)	4 (1.3)
Q20	have you been worried about not being able to have a bowel movement?	0 (0.0)	15 (4.8)	144 (46.5)	148 (47.8)	3 (0.9)
Q21	have you been more and more bothered by not being able to have a bowel movement?	2 (0.7)	11 (3.5)	146 (47.1)	148 (47.8)	3 (0.9)
The next questions assess your life with constipation. How much of the time, during the past 2 weeks...		**None of the time (0)**	**A little of the time (1)**	**Some of the time (2)**	**Most of the time (3)**	**All of the time (4)**
		n (%)				
Q22	have you been afraid that your condition will get worse?	4 (1.3)	9 (2.9)	141 (45.5)	153 (49.4)	3 (0.9)
Q23	have you felt that your body was not working properly?	4 (1.3)	9 (2.9)	131 (42.2)	163 (52.6)	3 (0.9)
Q24	have you had fewer bowel movements than you would like?	4 (1.3)	10 (3.2)	119 (38.4)	174 (56.2)	3 (0.9)
The next questions assess how satisfied you are. To what extent, during the past 2 weeks…		**Not at all (0)**	**A little bit (1)**	**Moderately (2)**	**Quite a bit (3)**	**Extremely (4)**
		n (%)				
Q25	have you been satisfied with how often you open your bowels?	30 (9.7)	141 (45.5)	102 (32.9)	37 (11.9)	0 (0.0)

The following questions are related to symptoms of constipation. During the past two weeks, to what extent or intensity...		Not at all (0)	A little bit (1)	Moderately (2)	Quite a bit (3)	Extremely (4)
		n (%)				
Q26	have you been satisfied with the regularity with which you open your bowels?	29 (9.3)	144 (46.5)	77 (24.8)	60 (19.4)	0 (0.0)
Q27	have you been satisfied with your bowel function?	24 (7.7)	145 (46.8)	81 (26.1)	60 (19.4)	0 (0.0)
Q28	have you been satisfied with your treatment?	35 (11.3)	110 (35.5)	90 (29.0)	75 (24.2)	0 (0.0)

(Insert Table 2 here)

Table 3 presents the correlation coefficients between the sub-scales of the PAC-QoL questionnaire including physical discomfort, psychological discomfort, worries and discomfort, treatment satisfaction, and the total score. The correlations between these scales were all positive and significant, indicating that increase in one factor is associated with increase into the others. The strong positive correlations among the PAC-QoL sub-scales indicate that higher levels of physical, psychological, and treatment-related discomfort are associated with each other, and potentially may lead to a poorer overall QoL of patients under MAT. These findings highlight the interconnectedness of different aspects of discomfort and satisfaction in the context of constipation-related QoL. (Insert Table 3 here).

Table 3
Pearson correlation coefficients among PAC-QoL sub-scales and the total score.

Physical discomfort	Physical discomfort	Psychological discomfort	Worries and discomfort	Treatment satisfaction	Total
	1	**0.73**	**0.54**	**0.65**	**0.77**
Psychological discomfort	0.73	1	0.85	0.64	0.92
Worries and discomfort	0.54	0.85	1	0.73	0.84
Treatment satisfaction	0.65	0.64	0.73	1	0.95
Total	0.77	0.92	0.95	0.84	1

Regarding test-retest reliability assessed by ICCs between the baseline and Phase 2, no change was observed in overall severity of constipation since ICC was 0.90 for the overall PAC-QOL scale ranging from 0.73 to 0.92 for the four subscales (Table 4). Therefore, using patient ratings of "no change" to

define a stable cohort, the PAC-QoL scales exceeded the 0.70 criterion for reliability. Moreover, the completion rates of the tests and retests were excellent. No missing data were found.

Table 4
Total and PAC-QoL factors test-retest reliability

Sub-scales	Question of the PAC-QoL	Mean ± SD	Cronbach's alpha	ICC
Physical discomfort	Q1-Q4	3.41 ± 0.5	0.85	0.73
Psychosocial discomfort	Q5-Q12	3.44 ± 0.5	0.93	0.92
Worries and Discomfort	Q13-Q23	2.77 ± 0.7	0.95	0.83
Treatment satisfaction	Q24-Q28	3.43 ± 0.5	0.91	0.90
Total	Q1-Q28	3.31 ± 0.4	0.96	0.90
Q: Questions of the PAC-QoL instrument; ICC: Intraclass correlation coefficient; SD: Standard deviation				

Regarding content validity, the I-CVI was 1.00 for all items of the questionnaire, a finding that indicates a strong content validity. Internal consistency evaluation per sub-scale and per item are presented in Tables 5 and 6 respectively. The Cronbach's alpha equal to a high value of 0.96 indicates an excellent internal consistency (Table 5). Each question of the PAC-QoL demonstrated a good item-scale correlation, with values generally higher than 0.4, confirming the homogeneity of the items (Table 6). Analysis of the ceiling and floor effects revealed that multiple PAC-QoL items exhibited considerable ceiling effects, with several items - such as Q24 (57.0%), Q23 (53.3%), and Q8 (53.7%), exceeding the 15% threshold commonly used to flag this issue. This suggests a limitation in the instrument's ability to capture improvement in QoL among patients already reporting high levels of discomfort or dissatisfaction. Conversely, floor effects were negligible, with all items falling below the 15% cut-off (typically under 2%). (Insert Tables 5 and 6 here).

Table 5
The results for the ceiling/floor effect, along with the Cronbach's alpha and item-scale correlation per PAC-QoL sub-scale and total score.

Sub-scales	Ceiling effect	Floor effect	Cronbach's a
Physical discomfort	0.26	0.01	0.85
Psychological discomfort	0.20	0.003	0.93
Treatment satisfaction	0.03	0.003	0.91
Worries and discomfort	0.01	0.003	0.95
Total	0.01	0.003	0.96

Table 6
The results for the ceiling/floor effect, along with Cronbach's alpha and item-scale correlation of the PAC-QoL.

Question of the PAC-QoL	Ceiling effect	Floor effect	Item Cronbach's alpha if item deleted	Item-scale correlation with correction for item-scale overlap
Q1	0.01	0.04	0.968	0.67
Q2	0.50	0.03	0.968	0.75
Q3	0.43	0.01	0.969	0.68
Q4	0.42	0.01	0.969	0.75
Q5	0.45	0.01	0.968	0.67
Q6	0.47	0.01	0.968	0.73
Q7	0.53	0.006	0.968	0.75
Q8	0.53	0.01	0.968	0.82
Q9	0.45	0.01	0.968	0.76
Q10	0.45	0.01	0.968	0.72
Q11	0.52	0.01	0.968	0.79
Q12	0.52	0.01	0.967	0.84
Q13	0.51	0.006	0.968	0.72
Q14	0.01	0.01	0.967	0.81
Q15	0.43	0.01	0.967	0.83
Q16	0.01	0.02	0.967	0.89
Q17	0.01	0.02	0.967	0.81
Q18	0.01	0.01	0.968	0.71
Q19	0.45	0.003	0.968	0.77
Q20	0.47	0.04	0.968	0.81
Q21	0.48	0.006	0.967	0.84
Q22	0.50	0.01	0.968	0.78
Q23	0.53	0.01	0.967	0.79
Q24	0.57	0.01	0.967	0.51
Q: Question				

Question of the PAC-QoL	Ceiling effect	Floor effect	Item Cronbach's alpha if item deleted	Item-scale correlation with correction for item-scale overlap
Q25	0.11	0.02	0.968	0.85
Q26	0.20	0.02	0.969	0.84
Q27	0.20	0.02	0.969	0.86
Q28	0.33	0.003	0.969	0.83
Q: Question				

Concerning to construct validity as indicated by the results of CFA, the four sub-scales of PAC-QoL fitted the data well. The CFI, TLI and the RMSEA values were equal to 0.90, 0.89 and 0.6 respectively. The KMO value was equal to 0.62 and Bartlett's criterion was statistically significant ($p < 0.001$) as well. The results of the correlations between PAC-QoL with BSFS and NHP dimensions in order to assess convergent validity, are presented in Table 7. The PAC-QoL showed significant negative correlations with various dimensions of the NHP, indicating that higher PAC-QoL scores were associated with lower quality of life. Similarly, concerning the correlation of PAC-QoL with BSFS, patients with stool Type 1 (separate hard lumps**)** experienced significantly higher levels of physical ($p = 0.01$) and psychological discomfort ($p = 0.03$) confirming that severe constipation was correlated with an increase in discomfort. Furthermore, patients with stool Type 2 (sausage shape but lumpy) experienced significant lower satisfaction with treatment. In addition, significant differences in treatment satisfaction ($p = 0.01$), worries and discomfort ($p = 0.01$), and the total PAC-QoL score ($p = 0.02$) were found in patients with stool Type 3 (like a sausage with cracks on the surface) suggesting that patients with this stool type which is closer to normal, tend to have better overall quality of life and treatment satisfaction. (Insert Table 7 here).

Table 7
Correlation between PAC-QoL with NHP and BSFS instruments

PAC-QoL										
	Ph.D		**Ps.D**		**TS**		**WD**		**Total PAC-QoL**	
NHP	p	r*	p	r*	p	r*	p	r*	p	r*
ADL	**< 0.001**	-0.23	**< 0.001**	-0.37	**0.01**	-0.13	**< 0.001**	-0.31	**< 0.001**	-0.30
ER	**< 0.001**	-0.25	**< 0.001**	-0.36	**< 0.001**	-0.26	**< 0.001**	-0.36	**< 0.001**	-0.36
EL	**< 0.001**	-0.28	**< 0.001**	-0.43	**< 0.001**	-0.35	**< 0.001**	-0.41	**< 0.001**	-0.43
P	**0.001**	-0.18	**< 0.001**	-0.26	**0.02**	-0.13	**0.01**	-0.13	**< 0.001**	-0.19
PA	**0.004**	-0.16	**< 0.001**	-0.27	0.31	-0.05	**0.002**	-0.17	**0.001**	-0.18
SL	**< 0.001**	-0.29	**< 0.001**	-0.37	**< 0.001**	-0.28	**< 0.001**	-0.35	**< 0.001**	-0.37
SI	**< 0.001**	-0.33	**< 0.001**	-0.38	**< 0.001**	-0.29	**< 0.001**	-0.39	**< 0.001**	-0.40
NHP Total	**< 0.001**	-0.32	**< 0.001**	-0.46	**< 0.001**	-0.29	**< 0.001**	-0.41	**< 0.001**	-0.43
BSFS	p	t**	p	t**	p	t**	p	t**	p	t**
Type 1	**0.01**	-2.45	**0.03**	-2.09	0.67	-0.42	0.07	-1.80	0.07	-1.80
Type 2	0.53	0.62	0.19	-1.30	**0.02**	-2.27	0.06	-1.91	0.09	-1.69
Type 3	0.40	0.82	0.06	1.85	**0.01**	2.45	**0.01**	2.37	**0.02**	2.30
Type 4	0.95	0.05	0.47	0.71	0.75	-0.31	0.35	0.92	0.61	0.50
Type 5	0.40	-0.83	0.65	0.44	0.78	-0.27	0.96	-0.04	0.93	-0.08
Type 6	0.40	0.82	0.90	-0.11	0.45	0.74	0.75	0.30	0.67	0.41

PAC-QoL: Patient assessment constipation quality of life; NHP: Nottingham health profile; BSFS: Bristol stool form scale; ADL: Activities of daily living; ER: Emotional reactions; EL: Energy level; P: Pain; PA: Physical abilities; SL: Sleep; SI: Social isolation; Ph.D: Physical discomfort; Ps.D: Psychological discomfort; TS: Treatment satisfaction; WD: Worries and Discomfort; *Pearson correlation; **t-test; Bold numbers indicate statistically significant correlation ($p < 0.05$).

PAC-QoL										
	Ph.D		Ps.D		TS		WD		Total PAC-QoL	
Type 7	0.51	0.65	0.25	1.14	0.21	1.23	0.38	0.87	0.26	1.12

PAC-QoL: Patient assessment constipation quality of life; NHP: Nottingham health profile; BSFS: Bristol stool form scale; ADL: Activities of daily living; ER: Emotional reactions; EL: Energy level; P: Pain; PA: Physical abilities; SL: Sleep; SI: Social isolation; Ph.D: Physical discomfort; Ps.D: Psychological discomfort; TS: Treatment satisfaction; WD: Worries and Discomfort; *Pearson correlation; **t-test; Bold numbers indicate statistically significant correlation ($p < 0.05$).

The impact of PAC-QoL on patients under MMT and BMT along with the effect size is depicted in Table 8. Patients under methadone reported significant higher levels of discomfort and higher treatment dissatisfaction compared to those under buprenorphine in all factors of the instrument. Furthermore, Cohen's d values were all higher than 0.8, indicating that the differences between the MMT and BMT patients were not just statistically significant, but also represented large to very large effects in practice. (Insert Table 8 here).

Table 8
Differences on PAC-QoL per sub-scale and total mean score between MMT and BMT patients as measured by the t-test and Cohen's d.

Sub-scales	MMT	BMT	p*	d**
	Mean ± SD	Mean ± SD		
Physical discomfort	3.60 ± 0.5	3.18 ± 0.3	**< 0.001**	0.92
Psychological discomfort	3.63 ± 0.5	3.20 ± 0.3	**< 0.001**	0.93
Worries and discomfort	3.67 ± 0.5	3.14 ± 0.3	**< 0.001**	1.15
Treatment satisfaction	3.16 ± 0.7	2.31 ± 0.4	**< 0.001**	1.30
Total	3.51 ± 0.6	2.96 ± 0.5	**< 0.001**	0.94

MMT: Methadone maintenance treatment; BMT: Buprenorphine maintenance treatment; SD: Standard deviation; *t-test measurement; **Cohen's d effect size; Bold numbers indicate statistically significant correlation ($p < 0.05$).

Discussion

The present investigation reports for the first time, the validation of PAC-QoL instrument for the evaluation of constipation due to opioid use in patients under MAT with methadone and buprenorphine. The instrument is a concise questionnaire, friendly to use and it can be completed in approximately 15 min covering the factors that mediate in constipation presence affecting QoL due to MAT. The self-reported PAC-QoL tool, except the original English version, has been validated in many languages, such as French, Turkish, Hindi, Japanese, and Dutch (Marquis et al., 2005; Mishra et al., 2021; Mokhtare et al.,

2017; Nikjooy et al., 2018). Moreover, the present PAC-QoL instrument is both reliable and valid for the constipation assessment in patients under MAT featuring its interconnectedness with QoL.

According to the results presented herein, the high correlation between the sub-scales of PAC-QoL that was observed, confirms the interconnectedness of OIC with QoL, since higher constipation is related with poorer QoL. This finding is consistent with previous evidence, wherein a high prevalence of constipation in patients who are under both methadone and buprenorphine has been revealed, along with a reduction of QoL that was associated with abdominal discomfort, psychological distress, problematic work productivity and social life impairment (Argoff, 2020; Lugoboni et al., 2016; Sason et al., 2021). Furthermore, patients with prolonged opioid use under MAT exert a poor QoL accompanied by stress, sleep dysregulation, malnutrition and overweight status that are also linked with chronic constipation (Chang et al., 2023; Huang et al., 2017; Jia et al., 2022; Leventelis et al., 2025b; Serdarevic et al., 2017).

Concerning the reliability of the present version of PAC-QoL, a strong internal consistency was revealed by estimating the Cronbach' s alpha coefficient for the tool subscales and the tool in total. In addition, no changes in total Cronbach' s alpha score were observed if an item was deleted. These results were comparable with previous published versions of the instrument, wherein Cronbach's alpha coefficient was ranged between 0.91 and 0.97 (Mokhtare et al., 2017; Nikjooy et al., 2018). Furthermore, ICC scores for test-retest reliability assessment measuring changes over time, were ranged from 0.73 to 0.92 for the sub-scales, and 0.90 for the total questionnaire, hence, featuring the good stability of the present PAC-QoL instrument. This fact was in line with other versions of the tool, such as Persian, Indian, Japanese and Turkish version as well (Bengi et al., 2015; Mishra et al., 2021; Nikjooy et al., 2018; Tsunoda et al., 2016). Moreover, given that no specific medication was used for OIC treatment, patients in the present investigation reported a great impact of constipation on satisfaction (Q25-Q28) suggesting that the majority of the patients were dissatisfied with the bowel movements and with the activity of MAT in digestive system. In fact, even though constipation is considered an under-treated symptom in addiction, however studies have shown that constipation might be an important side-effect of both methadone and buprenorphine, and might be associated with opioid use before entering MAT programs (Sason et al., 2021).

With respect to validation procedure, given that the I-CVI was equal to 1.00, the content validity of the present PAC-QoL scale was ensured determining that the instrument is valid to measure health condition and to guide a clinical decision process for constipation treatment (Almanasreh et al., 2019). Furthermore, no floor effect was revealed, since all items were measured under 15% cut-off, whilst a substantial ceiling effect in questions Q23, Q24, and Q8 was observed suggesting the limitation of the instrument to perceive differences in QoL among participants who felt high level of disappointment. This result comes in contrast with previous findings, wherein no ceiling or floor effect has been observed (Nikjooy et al., 2018). Noteworthy, the present investigation was carried out in a special population with many health problems, whereas the previous validation studies were conducted in volunteers of the general population with constipation under treatment. However, Q23 is referred to the frequency the

patients felt because their body has not been working properly during the last 2 weeks and Q24 about irregularity of bowel movements than they would like to have at the same time interval. Of note, the majority of the participants answered with grade 3 “most of the time”, in a percentage 52.6% and 56.2% for Q23 and Q24, respectively. These results indicate that patients under MAT were affected by the irregularity of their bowel condition which seems to play a pivotal role in their QoL. Previous findings have shown that patients with chronic constipation are more vulnerable due to less bowel movement, hence, being irritable in daily leaving (Bengi et al., 2015). For the decreased appetite during the last 2 weeks (i.e., Q8), 52.9% of the volunteers answered with grade 3 “quite a bit” which is in line with literature as it has been reported high prevalence of decreased appetite in MAT patients (Haber et al., 2017).

Furthermore, according to the CFA, the correlations between items were strong enough, and the items were appropriately grouped in the four sub-scales of the present version. In regards to convergent validity, the PAC-QoL instrument was significantly correlated with NHP in almost all sub-scales, and in total scores indicating that the higher constipation comes with the lower QoL. Similarly, when PAC-QoL was compared with BSFS, the findings demonstrated significant correlation especially between “physical” and “psychological discomfort” with stool Type 1, and “treatment satisfaction” with stool Type 2, indicating a severe constipation. In addition, the sub-scales “treatment satisfaction”, “worries and discomfort” and the total score were found to be significant correlated with stool Type 3, which is close to normal revealing that patients with this stool Type have experienced a better QoL. These results demonstrated an excellent construct validity and were also in line with previous validation studies in Japanese, French, Dutch, and English versions of the PAC-QoL instrument (Tsunoda et al., 2016). Both substances, due to their opioid nature, are known to inhibit gastric emptying, and decreased gastrointestinal tract peristalsis resulting in increased adsorption of fluid, and hence, leading to hard stools and constipation (Leppert, 2012), mainly in patients under MMT (Lugoboni et al., 2016).

Indeed, the present results revealed that patients under methadone suffered more severely by constipation than their counterparts under BMT, which is also confirmed by the effect size calculation with Cohen’s d value being higher than 0.8 indicating that this difference between two groups existed in practice. The high effect size ranging from 0.92 to 1.30 for the sub-scales and 0.94 for the total was shown the ability of PAC-QoL instrument to detect changes over time identifying relapse or improvement in constipation associated with QoL. These findings were in consistency with the original English version along with French and Dutch adaptations as well (Marquis et al., 2005). Furthermore, the high prevalence of constipation in MMT patients that was observed in the present investigation, comes in contrast to earlier findings, according to which constipation seems to be improved in MMT patients over time (Kreek, 1973; Langrod et al., 1981). Even though limited evidence exists comparing methadone and buprenorphine in terms of bowel side effects, the difference that was observed in the present investigation could be potentially related to the pathophysiological mechanism of action of these two substances, since methadone acts as a full agonist of MORs and buprenorphine as a MORs partial agonist and KORs antagonist (Leventelis et al., 2025a; Quaglio et al., 2010). Previously findings have shown that blockade of KORs by an antagonist such as buprenorphine, was associated with a reduction

of MORs agonist results in the gastrointestinal tract by lowering incidence rate of constipation events (Chamouard et al., 1993; Yimer et al., 2025).

The present investigation comes with specific limitations. The number of females was lower than that of males because females consist a small proportion in MAT programs, hence, obviously lacking generalizability. In respect to the literature, females present more severe constipation than their male counterparts (Haber et al., 2017). Furthermore, the participants in this study belong in a vulnerable population with many health problems due to opioid use, thus, constipation may be an under-recognized side-effect, among all others that are usually highlighted.

Conclusion

The Greek version of the PAC-QoL examined herein demonstrated excellent validity and reliability properties and sufficiently fulfills the requirements to be implemented in research and clinical settings as a measure of health in patients with chronic constipation as those with OUDs under MAT. It can also serve as a useful tool for follow-up assessment in patients during constipation treatment for repeated measures. Furthermore, this PAC-QoL questionnaire is comparable to those in the other versions enhancing the possibility of carrying out international studies in multicentral research set-ups.

Declarations

Acknowledgments

This article was supported by the Organization Against Drugs (OKANA) and the Department of Nursing, University of Peloponnese, Greece.

Author contributions

Christonikos Leventelis contributed to the study conception and design. Material preparation and data collection were performed by Mpatsiari Eleni, Karoumpali Maria, Teleme Angeliki, Kampitsi Antzouletta. Data analysis was conducted by Petros T. Barmpas and Sotiris Tasoulis. The first draft of the manuscript was written by Christonikos Leventelis and Petros T. Barmpas. Supervision was performend by Aristidis S. Veskoukis

Ethical approval. This study was performed in line with the European Union guidelines under the 1975 Helsinki Declaration as revised in 2013 and was approved from the Institutional Review Board of the Organization Against Drugs (OKANA) (ref. number 44482-2/12/2020).

Informed Consent. A written informed consent for participation in the study and data publication was provided by all volunteers before the start of the experimental procedure.

Declaration of conflicting interest. The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data Availability. The data used to support the findings of this study are available from the corresponding author upon request.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of conflicting interests

The authors declare that they have no conflict of interest.

References

1. Almanasreh E, Moles R, Chen TF (2019) Evaluation of methods used for estimating content validity. Res social administrative pharmacy: RSAP 15(2):214–221. ttps://doi.org/10.1016/j.sapharm.2018.03.066
2. Argoff CE (2020) Opioid-induced constipation: A review of health-related quality of life, patient burden, practical clinical considerations, and the impact of peripherally acting μ-opioid receptor antagonists. Clin J Pain 36(9):716–722. ttps://doi.org/10.1097/AJP.0000000000000852
3. Aziz I, Whitehead WE, Palsson OS, Törnblom H, Simrén M (2020) An approach to the diagnosis and management of Rome IV functional disorders of chronic constipation. Expert Rev Gastroenterol Hepatol 14(1):39–46. ttps://doi.org/10.1080/17474124.2020.1708718
4. Bellini M, Tonarelli S, Barracca F, Rettura F, Pancetti A, Ceccarelli L, Ricchiuti A, Costa F, de Bortoli N, Marchi S, Rossi A (2021) Chronic Constipation: Is a Nutritional Approach Reasonable? Nutrients 13(10):3386. ttps://doi.org/10.3390/nu13103386
5. Bengi G, Yalçın M, Akpınar H, Keskinoğlu P, Ellidokuz H (2015) Validity and reliability of the patient assessment of constipation quality of life questionnaire for the Turkish population. Turkish J gastroenterology: official J Turkish Soc Gastroenterol 26(4):309–314. ttps://doi.org/10.5152/tjg.2015.0185
6. Chamouard P, Klein A, Martin E, Adloff M, Angel F (1993) Regulatory role of enteric kappa opioid receptors in human colonic motility. Life Sci 53(14):1149–1156. ttps://doi.org/10.1016/0024-3205(93)90551-d
7. Chang HM, Huang MC, Fang SC, Lin SK (2023) Quality of life and associated factors of heroin-dependent patients receiving methadone and buprenorphine maintenance treatment. Neuropsychopharmacol Rep 43(4):607–615. ttps://doi.org/10.1002/npr2.12402
8. Chumpitazi BP, Self MM, Czyzewski DI, Cejka S, Swank PR, Shulman RJ (2016) Bristol Stool Form Scale reliability and agreement decreases when determining Rome III stool form designations. Neurogastroenterol Motil 28(3):443–448. ttps://doi.org/10.1111/nmo.12738
9. DeVellis RF (2017) Scale Development: Theory and Applications, 4th edn. Sage, Thousand Oaks, CA

10. Farmer AD, Drewes AM, Chiarioni G, De Giorgio R, O'Brien T, Morlion B, Tack J (2019) Pathophysiology and management of opioid-induced constipation: European expert consensus statement. United Eur Gastroenterol J 7(1):7–20. ttps://doi.org/10.1177/2050640618818305
11. Haber PS, Elsayed M, Espinoza D, Lintzeris N, Veillard AS, Hallinan R (2017) Constipation and other common symptoms reported by women and men in methadone and buprenorphine maintenance treatment. Drug Alcohol Depend 181:132–139. ttps://doi.org/10.1016/j.drugalcdep.2017.09.024
12. Hu LT, Bentler PM (1999) Cutoff Criteria for Fit Indexes in Covariance Structure Analysis: Conventional Criteria versus New Alternatives. Struct Equ Model 6:1–55. ttp://dx.doi.org/10.1080/10705519909540118
13. Huang L, Jiang H, Zhu M, Wang B, Tong M, Li H, Lin MB, Li L (2017) Prevalence and Risk Factors of Chronic Constipation Among Women Aged 50 Years and Older in Shanghai, China. Med Sci monitor: Int Med J experimental Clin Res 23:2660–2667. ttps://doi.org/10.12659/msm.904040
14. Jia S, Guo X, Chen Z, Li S, Liu XA (2022) The roles of the circadian hormone melatonin in drug addiction. Pharmacol Res 183:106371. ttps://doi.org/10.1016/j.phrs.2022.106371
15. Kandhi S, Chinta S, Urena Neme AP, Victoria Guerrero M, Rodriguez Guerra MA (2022) Acute Hydronephrosis Secondary to Methadone-Induced Constipation. Cureus 14(5):e25090. ttps://doi.org/10.7759/cureus.25090
16. Khangura SD, Ryce A (2021) Laxatives and Erectile Dysfunction Medications to Treat Side Effects of Opioid Agonist and Methadone Maintenance Therapy. Canadian Agency for Drugs and Technologies in Health
17. Kim H, Ku B, Kim JY, Park YJ, Park YB (2016) Confirmatory and Exploratory Factor Analysis for Validating the Phlegm Pattern Questionnaire for Healthy Subjects. *Evidence-based complementary and alternative medicine: eCAM*, *2016*, 2696019. ttps://doi.org/10.1155/2016/2696019
18. Kreek MJ (1973) Medical safety and side effects of methadone in tolerant individuals. JAMA 223(6):665–668
19. Langrod J, Lowinson J, Ruiz P (1981) Methadone treatment and physical complaints: a clinical analysis. Int J Addict 16(5):947–952. ttps://doi.org/10.3109/10826088109038903
20. Leppert W (2012) The impact of opioid analgesics on the gastrointestinal tract function and the current management possibilities. Contemp Oncol (Poznan Poland) 16(2):125–131. ttps://doi.org/10.5114/wo.2012.28792
21. Leventelis C, Barmpas PT, Kampitsi A, Iliopoulou K, Toutouktsi N, Malakopoulos P, Tasoulis S, Veskoukis AS (2025b) Pomegranate juice consumption improves sleep quality and melatonin concentration of patients with opioid use disorders under medication-assisted treatment with methadone and buprenorphine: A randomized controlled trial. Subst use Addict J 46(4):981–993. ttps://doi.org/10.1177/29767342251342666
22. Leventelis C, Goutzourelas N, Kortsinidou A, Spanidis Y, Toulia G, Kampitsi A, Tsitsimpikou C, Stagos D, Veskoukis AS, Kouretas D (2019) Buprenorphine and Methadone as Opioid Maintenance

Treatments for Heroin-Addicted Patients Induce Oxidative Stress in Blood. *Oxidative medicine and cellular longevity*, *2019*, 9417048. ttps://doi.org/10.1155/2019/9417048

23. Leventelis C, Koutsilieris M, Geitona M, Malliori M, Zyga S, Rojas Gil AP, Tzavella F, Georgoulopoulou E, Koutsopoulou E, Kampitsi A, Tsironi M (2020) Quality of Life in Patients under Substitution Treatment with Methadone and Buprenorphine. J Addict Behav Therapy Rehabilitation 9:4
24. Leventelis C, Veskoukis AS, Gil R, Papadopoulos AP, Garderi P, Angeli M, Kampitsi A, A., Tsironi M (2025a) Methadone and buprenorphine as medication for addiction treatment diversely affect inflammation and craving depending on their doses. Pharm (Basel Switzerland) 13(2):40. ttps://doi.org/10.3390/pharmacy13020040
25. Lugoboni F, Mirijello A, Zamboni L, Faccini M, Casari R, Cossari A, Gasbarrini A, Addolorato G, On Behalf Of Gics (2016) High prevalence of constipation and reduced quality of life in opioid-dependent patients treated with opioid substitution treatments. Expert Opin Pharmacother 17(16):2135–2141. ttps://doi.org/10.1080/14656566.2016.1232391
26. Marquis P, De La Loge C, Dubois D, McDermott A, Chassany O (2005) Development and validation of the Patient Assessment of Constipation Quality of Life questionnaire. Scand J Gastroenterol 40(5):540–551. ttps://doi.org/10.1080/00365520510012208
27. Martinez AP, de Azevedo GR (2012) The Bristol Stool Form Scale: its translation to Portuguese, cultural adaptation and validation. Rev Latinoam Enferm 20(3):583–589. ttps://doi.org/10.1590/s0104-11692012000300021
28. Mishra S, Singh R, Satapathy S, Bhatnagar S (2021) Validity and Reliability of the Hindi Version of the Patient Assessment of Constipation Quality of Life Questionnaire in Cancer Patients on Opioids for Pain Management at Tertiary Care Center, India. Indian J Palliat Care 27(1):95–98. ttps://doi.org/10.4103/IJPC.IJPC_187_20
29. Mokhtare M, Ghafoori SM, Soltani-Kermanshahi M, Boghratian AH, Agah S, Sheikhvatan M (2017) Reliability and validity of the Persian version of patient assessment of constipation- quality of life (PAC-QOL) questionnaire. Gastroenterol Hepatol bed bench 10(4):289–294
30. Nikjooy A, Jafari H, Saba MA, Ebrahimi N, Mirzaei R (2018) Patient Assessment of Constipation Quality of Life Questionnaire: Translation, Cultural Adaptation, Reliability, and Validity of the Persian Version. Iran J Med Sci 43(3):261–268
31. Peckham AD, Griffin ML, McHugh RK, Weiss RD (2020) Depression history as a predictor of outcomes during buprenorphine-naloxone treatment of prescription opioid use disorder. Drug Alcohol Depend 213:108122. ttps://doi.org/10.1016/j.drugalcdep.2020.108122
32. Quaglio G, Pattaro C, Gerra G, Mezzelani P, Montanari L, Jarlais DC, Lugoboni F (2010) Buprenorphine in maintenance treatment: experience among Italian physicians in drug addiction centers. Am J addictions 19(3):222–230. ttps://doi.org/10.1111/j.1521-0391.2010.00040.x
33. Reed MK, Smith KR, Ciocco F, Hass RW, Cox AL, Kelly EL, Weinstein LC (2023) Sorting through life: evaluating patient-important measures of success in a medication for opioid use disorder (MOUD)

treatment program. Subst Abuse Treat Prev Policy 18(1):4. ttps://doi.org/10.1186/s13011-022-00510-1

34. Samokhvalov AV, Rehm J (2015) Opioid-induced constipation reversal in response to placebo in a patient with a history of IBS receiving methadone maintenance therapy. *BMJ case reports*, *2015*, bcr2015211954. ttps://doi.org/10.1136/bcr-2015-211954
35. Sason A, Adelson M, Schreiber S, Peles E (2021) The prevalence of constipation and its relation to sweet taste preference among patients receiving methadone maintenance treatment. Drug Alcohol Depend 225:108836. ttps://doi.org/10.1016/j.drugalcdep.2021.108836
36. Saxon AJ, Hser YI, Woody G, Ling W (2013) Medication-assisted treatment for opioid addiction: methadone and buprenorphine. J food drug Anal 21(4):S69–S72. ttps://doi.org/10.1016/j.jfda.2013.09.037
37. Serdarevic M, Osborne V, Striley CW, Cottler LB (2017) The association between insomnia and prescription opioid use: results from a community sample in Northeast Florida. Sleep Health 3(5):368–372. ttps://doi.org/10.1016/j.sleh.2017.07.007
38. Sizar O, Genova R, Gupta M (2023) Opioid-Induced Constipation. In *StatPearls*. StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK493184/
39. Souza AC, Alexandre NMC, Guirardello EB (2017) Psychometric properties in instruments evaluation of reliability and validity. Propriedades psicométricas na avaliação de instrumentos: avaliação da confiabilidade e da validade. *Epidemiologia e servicos de saude: revista do Sistema Unico de Saude do Brasil*, *26*(3), 649–659. ttps://doi.org/10.5123/S1679-49742017000300022
40. Strain EC, Bigelow GE, Liebson IA, Stitzer ML (1999) Moderate- vs high-dose methadone in the treatment of opioid dependence: a randomized trial. JAMA 281(11):1000–1005. ttps://doi.org/10.1001/jama.281.11.1000
41. Terwee CB, Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J, Bouter LM, de Vet HC (2007) Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol 60(1):34–42. ttps://doi.org/10.1016/j.jclinepi.2006.03.012
42. Tsunoda A, Yamada K, Takano M, Kusanagi H (2016) The translation and validation of the Japanese version of the patient assessment of constipation quality of life scale. Surg Today 46(4):414–421. ttps://doi.org/10.1007/s00595-015-1179-2
43. Vallat R (2018) Pingouin: statistics in Python. J Open Source Softw 3(31):1026. ttps://doi.org/10.21105/joss.01026
44. Yimer BB, Soomro M, McBeth J, Medina CRR, Lunt M, Dixon WG, Jani M (2025) Comparative risk of severe constipation in patients treated with opioids for non-cancer pain: a retrospective cohort study in Northwest England. BMC Med 23(1):288. ttps://doi.org/10.1186/s12916-025-04118-7
45. Zamanzadeh V, Ghahramanian A, Rassouli M, Abbaszadeh A, Alavi-Majd H, Nikanfar AR (2015) Design and Implementation Content Validity Study: Development of an instrument for measuring Patient-Centered Communication. J caring Sci 4(2):165–178. ttps://doi.org/10.15171/jcs.2015.017