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Non-pharmacological techniques complementary to sedation administration decrease pain and anxiety during gastrointestinal endoscopic procedures: a meta-analysis

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Abstract

Background We performed a meta-analysis to assess the effect of non-pharmacological techniques, such as virtual reality (VR) and music, as adjuncts to sedation administration during gastrointestinal (GI) endoscopic procedures.

Methods We performed a systematic review across MEDLINE and Cochrane Central Register libraries of randomized controlled trials (RCTs), published between 2014 and 2024, evaluating how non-pharmacological techniques affected patients' reported pain (primary outcome), and anxiety and satisfaction (secondary outcomes), during endoscopy. We performed pairwise meta-analyses and expressed the effect size on study outcomes. We assessed the quality of evidence using Grading of Recommendations Assessment, Development and Evaluation approach.

Results Twelve RCTs analyzing outcomes from 1511 patients (non-pharmacological techniques n=762; standard sedation n=749) were included. Compared to the sedation-only group, application of non-pharmacological techniques resulted overall in significantly lower pain as mean difference [MD] -1.02, 95% confidence interval [CI] -1.64 to -0.41; I^2=64%) and anxiety (MD -1.07, 95%CI -1.75 to -0.39; I^2=20%), with higher satisfaction (MD 1.67, 95%CI 0.50-2.84; I^2=94%). There was low confidence in the estimates, due to the possibility of performance and detection bias in the majority of the studies, and the high level of heterogeneity. This effect regarding reported pain was consistent for virtual reality (3 RCTs, n=241) and music (10 RCTs, n=1270): MD -1.05, 95%CI -1.74 to -0.37; I^2=0%, and MD -1.00, 95%CI -1.80 to -0.20; I^2=73%, respectively.

Conclusion Concomitant application of virtual reality and/or music as adjuncts to sedation administration during GI endoscopic procedures decreases pain and anxiety, at the same improving time patient satisfaction.

Keywords Music, virtual reality, non-pharmacological, endoscopy, pain

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Conflict of Interest: None

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Introduction

Sedation and analgesia administration during gastrointestinal (GI) endoscopy contributes to procedural quality and improves patient satisfaction, in everyday clinical practice [1]. GI endoscopy is perceived as uncomfortable and anxiety-provoking, while the risk of serious sedation-induced adverse events, i.e., cardiopulmonary reactions, is always imminent, especially in those of advanced age and with comorbidities [2,3]. Irrespective of the specific sedative drug used in procedural sedation, hypoxia, hypotension and bradycardia are the most frequently observed adverse events [4]; however, efficacious and safe combinations of sedative/analgesic medications that facilitate the performance

of GI endoscopy are readily available [5]. The need for intravenous access, potentially allergic reactions to medication, and time spent in the recovery area are drawbacks of pharmacological sedation.

Hence, the application of non-pharmacological interventions, such as listening to music or the use of virtual reality (VR) glasses, in addition to standard pharmacological sedation might be a valuable tool. Among these, music is perhaps the one with the most evidence available; however, its exact impact on patient-reported outcomes compared to standard care remains ambiguous, since individual studies and meta-analyses face flaws in their performance that have attracted criticism [6-8]. Furthermore, data regarding the role of currently available VR modalities are inconclusive. In this context, we performed an updated systematic review with meta-analysis incorporating data exclusively from recent randomized controlled trials (RCTs) to evaluate the effect of non-pharmacological interventions, namely music and VR, as adjuncts to conventional sedation administration on patients' reported outcomes for endoscopic procedures.

Materials and methods

This study was carried out according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [9] (Supplementary Table 1). The review protocol is available at the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420250650749.

Eligibility criteria

Eligibility criteria were defined according to the *PICO* statement; P: patients undergoing any type of GI endoscopic procedure; I: non-pharmacological techniques such as VR and/or music as adjuncts to standard sedation (excluding pre-endoscopy interventions such as education and training); C: standard sedation practice; and O: patients' reported outcomes (including pain, anxiety and satisfaction). Only RCTs, published as full text in the English language, were eligible for inclusion. Non-randomized, prospective or retrospective studies, pragmatic implementation trials, studies reporting secondary analysis of a previously published RCT, review studies and meta-analyses were excluded.

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Identification and selection of studies

Our search strategy included the terms "gastroscopy", "colonoscopy", "ERCP", "EUS", "virtual reality" and "music", as both medical subject headings (MeSH) and free-text terms combined with the Boolean set operators "AND" and "OR". PubMed and the Cochrane Central Register of Controlled Trials electronic databases were searched, starting from 1st January 2014 until 31st December 2024. The search was performed on 5th January 2025. Two investigators (PR and NDL) independently performed the search and after removal of duplicates, 2 reviewers (PR and NDL) assessed the titles and abstracts of all results for inclusion. Eligibility of selected articles was evaluated independently, using predesigned eligibility forms, with disagreements resolved by discussion. Finally, references of all eligible studies were manually searched by all reviewers, to identify potentially studies missed during the first search.

Data extraction and quality assessment

Data from eligible studies were independently extracted by 2 authors (PR and NDL) into a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA) using a standard data extraction form. These data included: name of first author, publication year, endoscopic procedures, number of total participants, mean reported pain, as per each scale assessed. We also extracted the reported anxiety and satisfaction scores, sedation/analgesia medication doses, as well as vital signs (systolic blood pressure, oxygen saturation and heart rate).

Assessment of risk of bias

The Cochrane collaboration's assessment tool was used to assess the risk of bias for each individual study included [10]. Two independent researchers (PR and GT) assessed the risk of bias attributed to methods used to generate the randomization schedule and conceal treatment allocation (selection bias), implementation of blinding for participants or personnel (performance bias), assessment of outcomes (detection bias), proportion of subjects who completed follow up (attrition bias), and evidence of selective reporting of outcomes (reporting bias). Each study included in the meta-analysis was classified as having high, low or unclear risk of bias, with reference to each of the abovementioned domains.

Clinical outcomes studied

The primary outcome of the meta-analysis was evaluation of the reported pain, when non-pharmacological techniques, such as VR or music, were applied complementary to standard sedation. Their effect on patient-reported anxiety and satisfaction, sedation/analgesia medication doses, as well

as vital signs (systolic blood pressure, oxygen saturation, and heart rate) comprised the secondary outcomes.

Data synthesis and statistical analysis

For continuous outcomes, we calculated the mean difference (MD) with 95% confidence interval (CI), using inverse variance. Data were meta-analyzed using the random-effects model (DerSimonian and Laird method) to allow a more conservative estimate of the effect, given the anticipated substantial methodological heterogeneity among studies. We assessed publication bias visually, by checking the funnel plot for asymmetry. All analyses were performed at the 0.05 significance level. Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) software package was used to meta-analyze all data and to construct forest and funnel plots.

Heterogeneity assessment and sensitivity analyses

We assessed the presence of heterogeneity using the χ^2 (Cochran Q) test and I^2 statistic. For I^2 values >50%, we undertook predefined sensitivity analysis to identify the source of heterogeneity by excluding 1 study at a time to explore potential sources of clinically relevant heterogeneity among the trials, as proposed by the Cochrane collaboration. One additional sensitivity analysis was undertaken for our primary outcome, namely per non-pharmacological technique (VR or music).

Assessment of quality of body of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to rate the certainty of evidence synthesized for each different outcome [11]. This graded inconsistency, risk of bias, indirectness, imprecision and publication bias. Overall quality was deemed very low, low, moderate, or high using GRADEpro (GRADE Working Group).

Results

Study selection

The initial search yielded 221 citations. Of these, 200 were excluded after title and abstract review as irrelevant to the study's aim, or as duplicates, leaving 21 articles eligible for full-text assessment. Three non-randomized studies, 5 where no sedation was delivered, and 1 study with a different endpoint (endoscopist performance instead of patient satisfaction) were excluded; thus, 12 studies [12-23] were included in the final analysis. The PRISMA flowchart showing the study selection is depicted in Fig. 1.

Characteristics of studies included

Table 1 summarizes the main characteristics of the included studies. One study assessed the effect of VR distraction methods [23], 9 studies assessed the effect of music therapy [12,14-19,21,22], while the effects of both auditory and visual distraction were assessed in 2 studies [13,20]. The vast majority of studies (n=11) enrolled individuals undergoing colonoscopy for various indications, while 1 study included patients undergoing diagnostic endoscopic ultrasound [17].

Methodological quality and risk of bias

A summarized assessment of the risk of bias per study using the Cochrane Collaboration's risk of bias assessment tool is illustrated in Fig. 2. Participating physicians and patients were blinded neither to the equipment used, nor to the outcomes measured, in the majority (n=9/12) of the studies; hence, we noted high concern regarding measurement bias.

Endpoints

Primary endpoint: pain

Eleven studies [12,13,15-23] provided data regarding reported pain during GI endoscopy. Overall, 1511 patients were included: 762 received non-pharmacological techniques while 749 received standard sedation. Compared to standard sedation, addition of non-pharmacological techniques resulted in significantly lower pain (MD -1.02; 95%CI -1.63 to 0.41; I^2=64%) (Fig. 3). In an effort to address heterogeneity, the step-by-step, leave-one-out sensitivity analysis showed that the pooled effect size remained significant after exclusion of any single study. When studies were assessed according to the modality used (VR or music), heterogeneity was eliminated (χ^2=0.77; Df=2; P=0.68) for the subgroup of studies analyzing VR technology [13,20,23], and the measured effect was further strengthened (MD -1.05, 95%CI -1.74 to -0.37; I^2=0%). Visual assessment of the funnel plot showed no evidence of publication bias (Supplementary Fig. 1), while the certainty of evidence derived from the meta-analysis indicated that quality of evidence supporting lower reported pain with non-pharmacological techniques was low, given the serious risk of bias, serious inconsistency and indirectness (Supplementary Table 2).

Secondary endpoints

Anxiety: Nine studies provided data regarding reported anxiety during GI endoscopy [12,14-16,18-20,22,23]. A total of 1255 patients were included in the analysis: 629 received non-pharmacological techniques while 626 received standard sedation. Compared to standard sedation, the addition of non-pharmacological techniques resulted in significantly lower

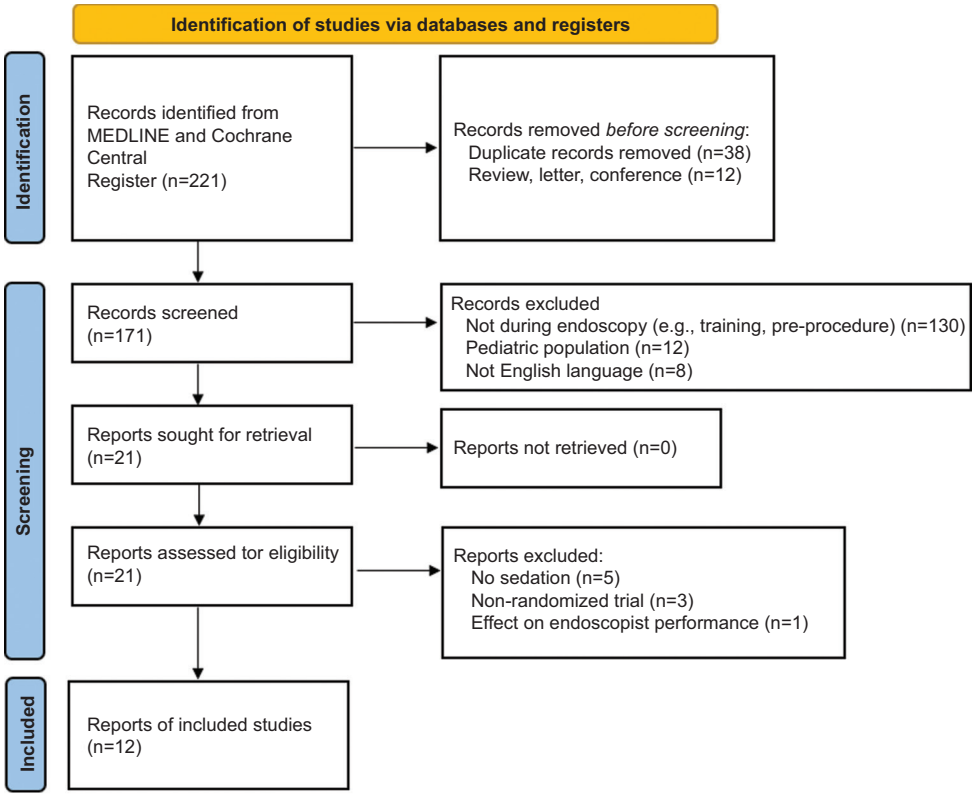

Figure 1 Flow diagram of assessment of eligible studies identified

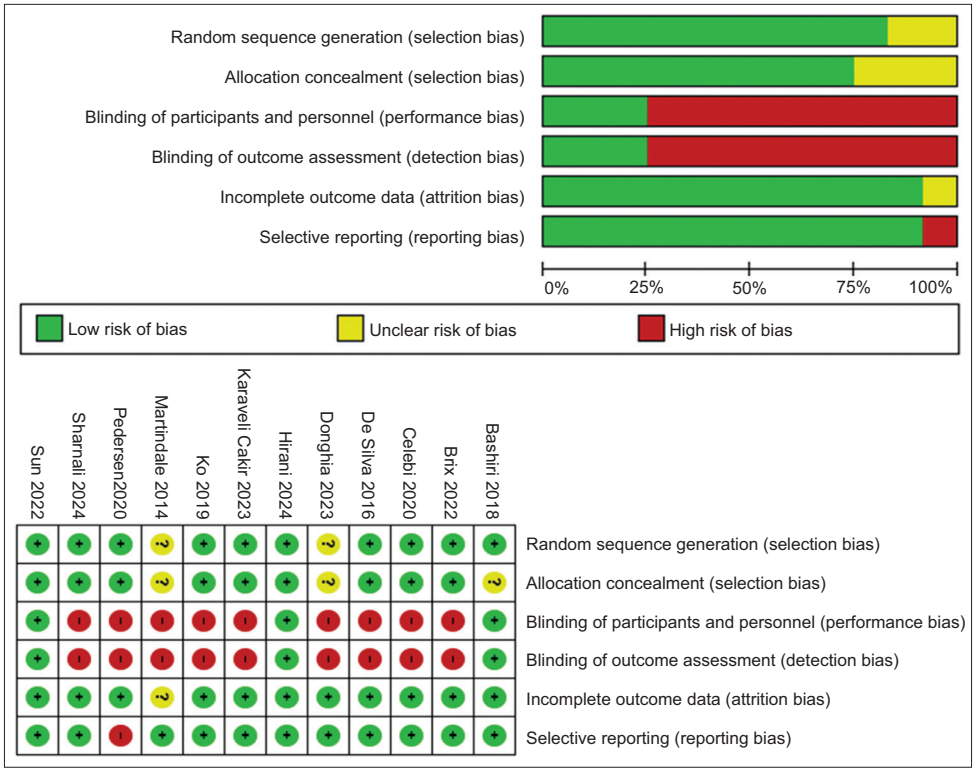

Figure 2 Risk of bias of included trials

Table 1 Characteristics of the included studies

Studies assessing the effect of VR

Study (Author, year) [ref.]	Country	No. of sites (no. of subjects)	Male sex (%)	Procedure	Intervention	Comparator	Pain scale used	Outcome in intervention arm	Outcome in comparator arm
De Silva, 2016* [13]	Sri Lanka	1 (n=200)	64	Colonoscopy	VR glasses (Watching film of their choice with sound using a head mounted display)	Standard sedation	VAS, with a score given from 0 to 10 (0=no pain to 10=very painful)	Pain VAS 4	Pain VAS 5
Cakir, 2023* [20]	Turkey	1 (n=120)	58.3	Colonoscopy	VR glasses (Watching with sound a licensed virtual reality application, "A walk on the beach," through an Android mobile phone)	Standard sedation	A 10-centimeter vertical VAS. Pain intensity scored between 0 and 10, absence of pain was "0" point, whereas the most severe pain scored "10."	Pain VAS 3.2 Anxiety 46.8 Satisfaction VAS 9.3	Pain VAS 4.1 Anxiety 49.7 Satisfaction VAS 7.5
Shamali, 2024 [23]	Denmark	1 (n=47)	42.6	Colonoscopy	VR glasses (visualized content of VR via headset, a 3-dimensional gear with a connected tablet)	Standard sedation	Self-reported 11-point numeric rating scale 0 (no pain) to 10 (highest imaginable pain) immediately before, during, and immediately after the procedure	Pain VAS 2.3 Anxiety 5.0 Satisfaction 9.7	Pain VAS 4.0 Anxiety 5.7 Satisfaction 8.7

Studies assessing the effect of music

Study (Author, year) [ref.]	Country	No. of sites (no. of subjects)	Male sex (%)	Procedure	Intervention	Comparator	Pain scale used	Outcome in intervention arm	Outcome in comparator arm
Martindale, 2014 [12]	Australia	1 (n=34)	47.1	Colonoscopy	Investigator-selected music (delivered via headphones attached to a MP3 player)	Standard sedation (headphones not plugged in to any device)	VAS designed for the study	Pain VAS 25.7 Anxiety 27.7 Satisfaction 76	Pain VAS 33.6 Anxiety 27.8 Satisfaction 80
De Silva, 2016* [13]	Sri Lanka	1 (n=200)	64	Colonoscopy	Music of their choice during colonoscopy (Sinhala, Hindi, classic or hip-hop songs)	Standard sedation	VAS, with a score given from 0 to 10 (0=no pain to 10=very painful)	Pain VAS 3	Pain VAS 5
Bashiri, 2018** [14]	Turkey	1 (n=58)	29.3	Colonoscopy/ EGD	Music (patient's favorite music administered through headphones) + moderate sedation	Moderate sedation (headphone was on without any music)	Numerical Rating Scale (0-10)	Anxiety 46.4	Anxiety 48.8

(*Contd...*)

Table 1 Characteristics of the included studies

Studies assessing the effect of VR									
Study (Author, year) [ref.]	Country	No. of sites (no. of subjects)	Male sex (%)	Procedure	Intervention	Comparator	Pain scale used	Outcome in intervention arm	Outcome in comparator arm
Bashiri, 2018*** [14]	Turkey	1 (n=96)	42.7	Colonoscopy/ EGD	Music (patient's favorite music administered through headphones) + deep sedation	Deep sedation (headphone was on without any music)	Numerical Rating Scale (0-10). All	Anxiety 45.4	Anxiety 47.6
Ko, 2019 [15]	Hong Kong	1 (n=80)	51.2	Colonoscopy	Easy listening popular Chinese songs (delivered via headphone attached to a MP3 player)	Standard sedation	NA	Anxiety 30.8 Satisfaction 8.6	Anxiety 30.0 Satisfaction 7.8
Çelebi, 2020 [16]	Turkey	1 (n=112)	50	Colonoscopy	Ajam Ashiran maqam (low and relaxing instrumental music), delivered via headphone attached to a MP3 player	Standard sedation	VAS, with a score given from 0 to 10 (0: no pain/no discomfort (very comfort), 10: the most severe pain/very uncomfortable (not comfortable at all)	Pain VAS 1.5 Anxiety 42.0	Pain VAS 4.0 Anxiety 48.5
Pedersen, 2020 [17]	Denmark	1 (n=126)	64.3	Rectal EUS	Music (non-lyrical music with 60-80 beats per minute via CD player)	Standard sedation	VAS, ranging from 0 (no pain) to 10 (maximum pain)	Pain VAS 2.0	Pain VAS 2.3
Brix, 2022 [18]	Denmark	1 (n=337)	52.5	Colonoscopy	Niels Eje's composition (instrumental acoustic music with integrated sounds of nature), delivered in the endoscopy suite	Standard sedation	Numerical rating scale (NRS) from 0=no pain and to 10=worst possible pain	Pain VAS 2 (men) Pain VAS 4 (women)	Pain VAS 2 (men) Pain VAS 3 (women)
Sun, 2022 [19]	China	1 (n=216)	51.9	Colonoscopy	Popular piano pieces with soft melody, moderate rhythm and no lyrics (delivered via headphone)	Standard sedation (headphone was on without playing music)	Pain scores were scored using visual analogue scores.	Pain 13.7 Anxiety 30.2 Satisfaction 86.2	Pain 20.6 Anxiety 33.2 Satisfaction 68.5
Cakir, 2023* [20]	Turkey	1 (n=120)	58.3	Colonoscopy	Music (delivered via headphone attached to a MP3 player)	Standard sedation	A 10-centimeter vertical VAS. Pain intensity scored between 0 and 10, absence of pain was 0 points, whereas the most severe pain scored 10.	Pain VAS 3.2 Anxiety 46.8 Satisfaction VAS 9.3	Pain VAS 4.1 Anxiety 49.7 Satisfaction VAS 7.5
Donghia, 2023 [21]	Italy	1 (n=62)	?	Colonoscopy	Preferred music (delivered using the Spotify™ (Stockholm, Sweden) app	Standard sedation	Pain severity rated on a numerical rating scale (NRS)	Pain VAS 2.6	Pain VAS 4.5
Hirani, 2024 [22]	Pakistan	1 (n=110)	62.7	Colonoscopy	Recordings of nature (birds, sea waves, forest, rainfall) combined with soft instruments (delivered via in-earphone attached to a MP3 player)	Standard sedation	A 10-centimeter vertical VAS. Pain intensity scored between 0 and 10; 0 points means no pain whereas 10 refers to worst pain	Pain VAS 3.0	Pain VAS 3.1

*Data from the arm where virtual reality was applied

VR, virtual reality; VAS, visual analog scale

*Data from the arm where music was applied; **Data from the arm where moderate sedation was applied; ***Data from the arm where deep sedation was applied

VAS, visual analog scale; EGD, esophagogastroduodenoscopy

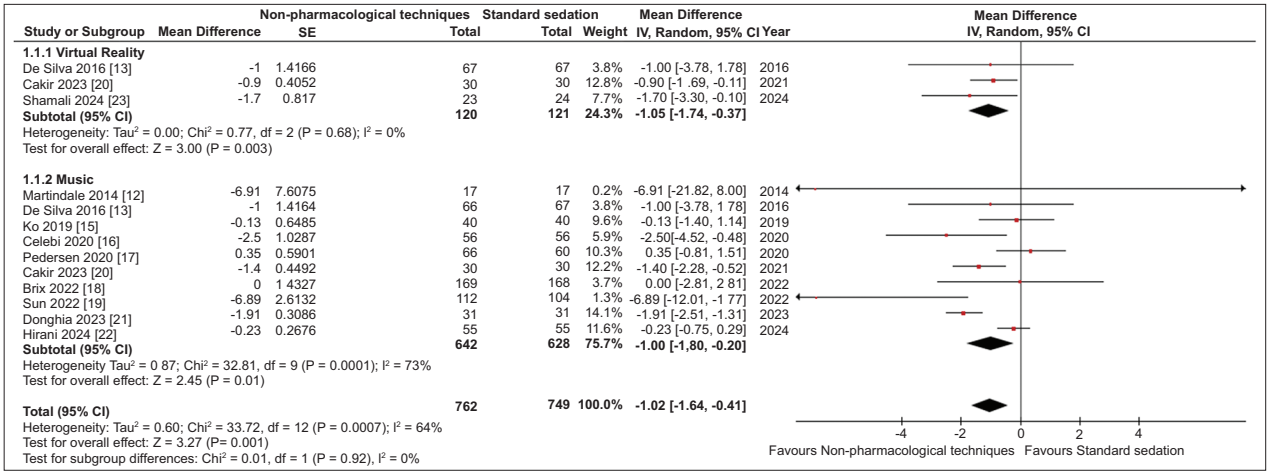

Figure 3 Forest plot for studies assessing the effect of non-pharmacological techniques complementary to sedation administration on reported pain
CI, confidence interval

anxiety (MD -1.07, 95%CI -1.75 to -0.39; I^2=20%) (Fig. 4A). Sensitivity analysis did not detect any study responsible for the detected heterogeneity. No evidence of publication bias was evident (data not shown).

Patient satisfaction: Six studies provided data regarding reported satisfaction during GI endoscopy [12,15,18-20,23]. This analysis included 834 patients: 421 underwent non-pharmacological techniques while 413 received standard sedation. Compared to standard sedation, the addition of non-pharmacological techniques resulted in significantly higher levels of satisfaction (MD 1.67, 95%CI 0.50-2.84; I^2=94%) (Fig. 4B). The sensitivity analysis, excluding 1 study at a time, did not identify a single study accountable for this effect. No evidence of publication bias was evident (data not shown).

Sedation/analgesia medication doses: Sedation/analgesia medication dosages were provided in 6 studies [12-14,18,22,23], referring to 891 patients: 438 underwent non-pharmacological techniques, while 453 received standard sedation. Additional non-pharmacological techniques were associated with a lower mean dose of midazolam compared to standard sedation, although the difference was non-significant (MD -0.43, 95%CI -0.88 to 0.02; I^2=93%) (Supplementary Fig. 2A). Similarly, the mean dose of analgesia did not differ significantly between the 2 arms (MD -1.41, 95%CI -4.14 to 1.32; I^2=51%) (Supplementary Fig. 2B). The sensitivity analysis, excluding 1 study at a time, did not identify a single study accountable for this effect. No evidence of publication bias was evident (data not shown).

Effect on vital signs during endoscopy

a) *Systolic blood pressure*. Data analysis from 6 studies [15,16,18-20,22] including outcomes from 975 patients (492 received non-pharmacological techniques while 483 received standard sedation), showed no significant difference with the use of the non-pharmacological techniques compared to standard sedation (MD -3.10, 95%CI -8.15 to 1.96; I^2=75%) (Supplementary Fig. 2C).
b) *Oxygen saturation*. Four studies analyzing outcomes from 785 patients (397 received non-pharmacological techniques while 388 received standard sedation), examined oxygen saturation [16,18-20]. No significant difference in oxygen saturation fluctuation between the non-pharmacological techniques and standard sedation was detected (MD 0.32, 95%CI -0.68 to 1.32; I^2=36%) (Supplementary Fig. 2D).
c) *Heart rate*. Data analysis from six studies [15,16,18-20,22], analyzing outcomes from 975 patients (492 received non-pharmacological techniques while 483 received standard sedation), showed no significant difference in heart rate between the use of the non-pharmacological techniques compared to standard sedation (MD -3.52, 95%CI -9.49 to 2.45; I^2=88%) (Supplementary Fig. 2E).

Grade evidence estimates

Overall, our confidence in the effect estimates for efficacy was deemed low. More specifically, we downgraded the quality of the body of evidence by 3 levels: 1 for the risk of performance and detection bias in the majority of the studies; 1 for inconsistency; and 1 for the presence of indirectness in the evidence—since the included studies were conducted in different settings (different populations, methods, endoscopists, patients' reported outcomes) (Supplementary Table 2).

Discussion

Sedation and analgesia have revolutionized the procedural quality of GI endoscopy, contributing at the same time to better patient satisfaction and more willingness to undergo an endoscopic procedure [3]. Over the last 10 years, digital access to music (and, to a lesser extent, to VR) has become widely and

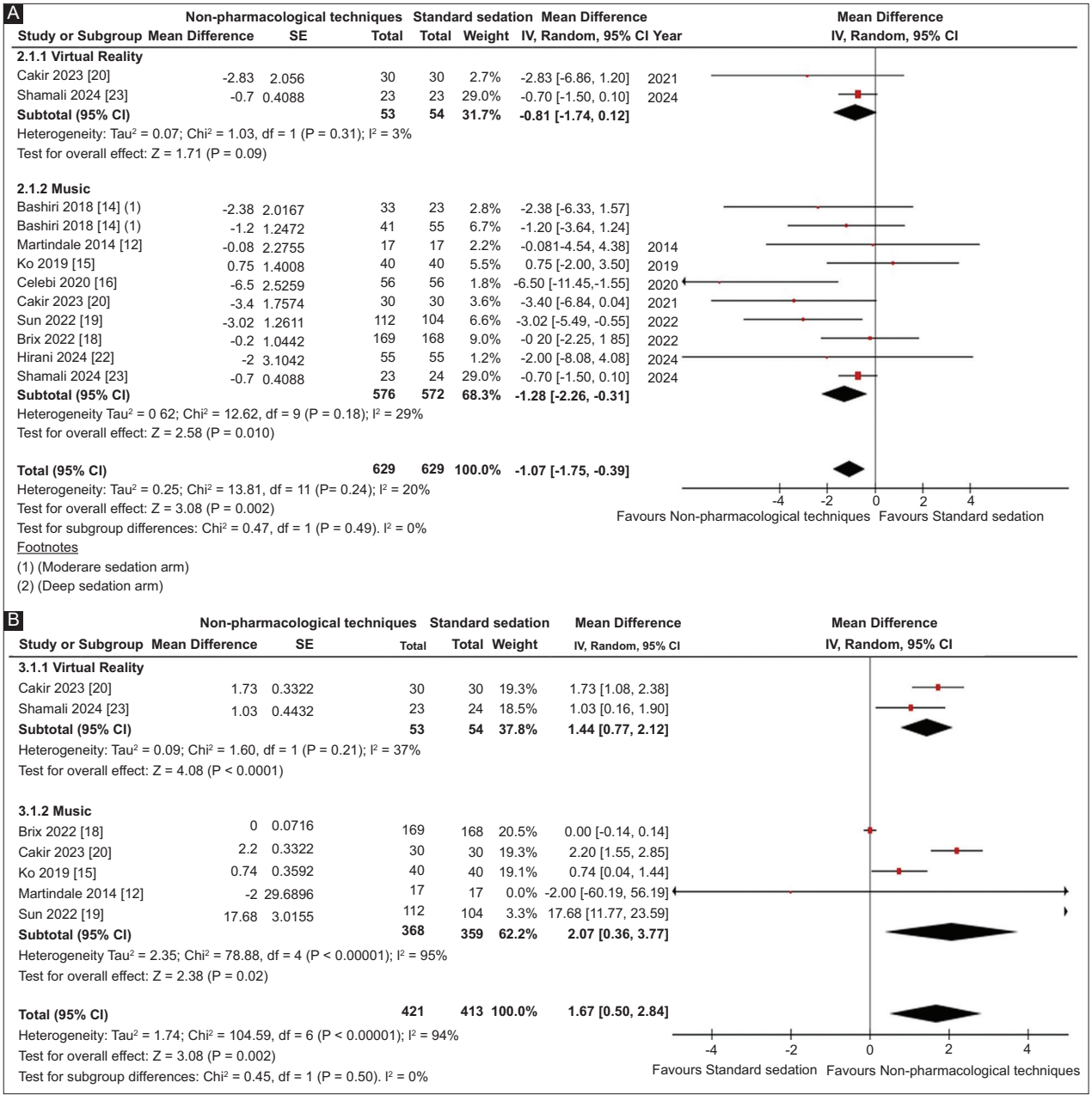

Figure 4 Forest plot for studies assessing the effect of non-pharmacological techniques complementary to sedation administration on reported (A) anxiety and (B) patient satisfaction
CI, confidence interval

easily available, with numerous online streaming platforms, and small portable devices such as music boxes and in-ear headphones.

Our systematic review and meta-analysis demonstrated that provision of music or VR complementary to standard sedation administration not only resulted in a significant decrease in patients' procedure-related pain levels, but also mitigated anxiety during the preprocedural period, leading to greater satisfaction. Notably, this effect was more prominent for VR than for music, implying that the heterogeneity derives principally from studies evaluating music; this could be attributed to the different types of music types, or to different modes of music application—i.e., headphones, music in room. However, further subgroup analyses to address this issue in detail were not possible, in view of the poor reporting. Changes in the visual analogue scale of more than 9 mm were found to be clinically significant, irrespective of sex, age or cause of pain [24]. As control of pain and anxiety is a high priority for patients [3], reductions in pain and anxiety are most likely to be clinically meaningful. Initially, no difference

was observed with patient-selected music [25]; more recently, however, patient-selected music appears to be more effective than researcher-selected music [26]. The involvement of the patient's contribution and choice is beneficial during the assessment and information gathering prior to endoscopic procedures [27,28].

Although confidence in the effect estimates was deemed low, our analysis showed a clear-cut benefit from application of the audiovisual distraction techniques in reducing pain and anxiety. Music can distract the patients' attention from pain and discomfort, but auditory distractions appear to be more effective than visual distractions in reducing the dose of sedation, indicating that music has a greater effect than mere distraction [29]. Music also awakens memories and emotions, further reducing levels of stress and anxiety [30]. Numerous brain areas (e.g., cingulate cortex, periaqueductal gray matter) and neurotransmitters (e.g., endorphins, oxytocin, dopamine) are involved in pain modulation [25,31], and can be modified by listening to music [32,33]. Besides neurotransmitters, other biological processes (noradrenaline, prostaglandins, cytokines, etc.) are also modified by music [31]. Music also facilitates recovery after psychological stress [34].

A handful of meta-analyses have attempted to pool data on the role of listening to music in reducing pain in adults undergoing colonoscopy [6-8,35]. These had conflicting results, but reported a small treatment effect in favor of music to improve overall patient experience, while the role of VR was not studied in those iterations.

Implementation of non-pharmacological techniques complimentary to standard sedation care during GI endoscopic procedures may have favorable implications for everyday clinical practice. These modalities are safe (no complications were reported), easy-to-administer, low-cost and noninvasive interventions, that can be applied in many different clinical settings, underlining the generalizability of their application, regardless of the physician's expertise, and without any previous dedicated training.

Despite the use of sedation/analgesia as an effective measure to reduce pain and discomfort, serious cardiorespiratory events may occur, especially in patients of advanced age and/or with comorbidities [36]. Optimized sedation not only improves the core quality indicators of the endoscopic procedure itself, but also decreases the burden on patients and endoscopy departments due to a prolonged recovery time [37]. Hence, the possibility of administering smaller quantities of sedatives and analgesic might potentially affect the incidence of cardiopulmonary reactions. Our analysis indeed showed lower levels of sedative medication used in the intervention arm, although the difference was statistically non-significant. Lower doses of sedative medication and/or a shorter recovery time could result in lower costs. In the case of VR goggles, the purchase price, as well as reprocessing and cleaning costs, need to be taken into account regarding cost-effectiveness, while listening to music via the patient's personal music device and/or earphones would most likely be cost-beneficial.

The principal strength of this meta-analysis is the use of a rigorous and reproducible methodology; we conducted a comprehensive recent literature search, reported in full, and with a strict assessment of study quality and evidence, following recommendations for systematic reviews [38]. Including only studies of the highest quality (RCTs), the exclusion of publication bias, as well as the performance of sensitivity analyses are additional study assets.

There are limitations related to both the analysis and the individual studies that merit further discussion. First, the high level of heterogeneity, the absence of participant blinding and allocation to the endoscopist, and the presence of confounding factors, leading to the low-grade certainty of the evidence, should be considered in any interpretation of the results of our analysis.

Second, there were differences in the technology systems used (i.e., different modes of music administration, different genres of music at the discretion of either the patient or the endoscopist), in the clinical settings (i.e., outpatient vs. inpatients), in the indications for endoscopy, and in the populations enrolled (regarding age distribution, and variations in lifestyle of people from different countries), all of which limited the ability to draw firm conclusions across the spectrum of non-pharmacological techniques. Notably, the primary outcome of interest (pain) was a patient-reported outcome evaluated by different scales in each study. Heterogeneity for the primary endpoint (pain, I^2=64%) was eliminated when studies were assessed according to the modality used (VR or music), implying that heterogeneity derived principally from studies evaluating music. This could be attributed to the different music types used, or to the different modes of delivery, i.e., headphones or music in room. However, further subgroup analyses to address this issue were not possible, given the poor reporting, and this should also be listed among the limitations of the current study. To address this, we used a random-effects model, allowing a more conservative effect of estimate when a high degree of heterogeneity among RCTs is expected. In addition, most of the included trials suffered bias related to performance and outcome detection, given that blinded assessment was not possible, while the subjectivity of the outcome measurements may have led to performance bias.

Third, a number of patient-, provider- and system-level factors (timing and duration of the intervention, frequency of exposure, timing of outcome variable assessment. level of endoscopist experience) may affect the performance of these technology systems. Finally, it was impossible to perform a cost-benefit analysis.

To conclude, we found that concomitant application of non-pharmacological techniques (VR or music) as adjuncts to standard sedation care for GI endoscopic procedures may result in reduced pain and anxiety, while also improving patient satisfaction.

Summary Box

What is already known:

- The risk of serious sedation-induced adverse events during gastrointestinal endoscopy is always imminent
- Application of non-pharmacological interventions, such as listening to music or the use of virtual reality glasses, in addition to standard pharmacological sedation might be valuable

What the new finding is:

- In a meta-analysis of twelve randomized controlled trials, the application of non-pharmacological techniques resulted in significantly lower pain and anxiety, while also improving patient satisfaction

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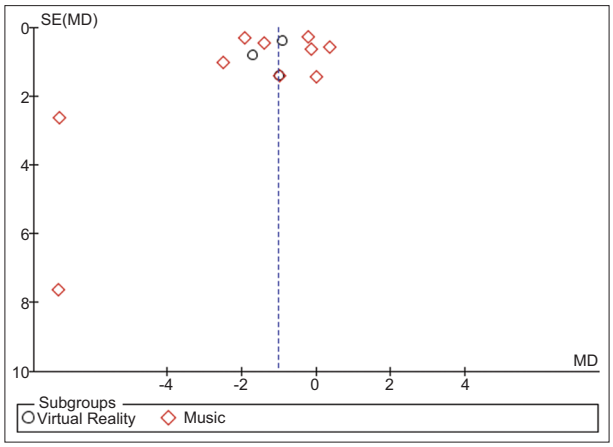
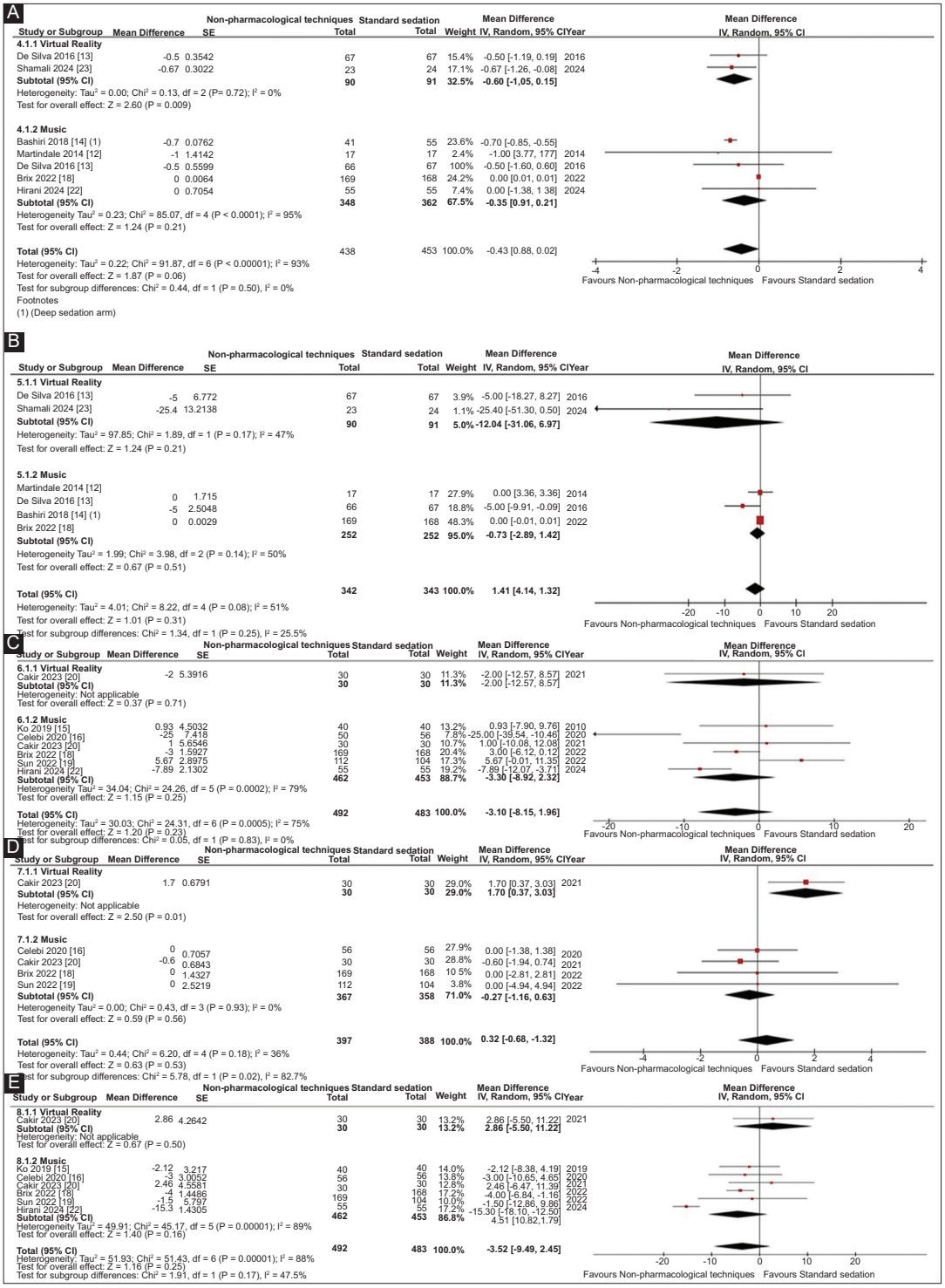
Supplementary material



Supplementary Figure 1 Funnel plot for studies assessing the effect of non-pharmacological techniques complementary to sedation administration on reported pain
SE, standard error; MD mean difference



Supplementary Figure 2 Forrest plot for studies assessing the effect of non-pharmacological techniques complementary to sedation administration on reported (A) dose of sedatives (midazolam); (B) dose of analgesics; (C) systolic pressure (mmHg); (D) oxygen saturation (%); (E) heart rate (beats per minute)

CI, confidence interval

Supplementary Table 1 PRISMA guidelines checklist

Section/topic	#	Checklist item	Reported on page #
		TITLE	
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
		ABSTRACT	
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4 CRD420250650749
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
		METHODS	
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6-7
Search	8	Present full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	6-7,
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
		RESULTS	
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow up period) and provide the citations.	10, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11 Figure 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-14

(*Contd*...)

Supplementary Table 1 (*Continued*)

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11 Figure 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-13
		DISCUSSION	
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
		FUNDING	
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

Supplementary Table 2 Quality of body of evidence - Summary of Findings Table (GRADE)

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision With placebo	Publication bias With Pain	Overall certainty of evidence	Study event rates (%)		Relative effect (95%CI)	Anticipated absolute effects	
							With placebo	With Pain		Risk with placebo	Risk difference with Pain
Reported Pain 1511 (11 RCTs)	Serious[a]	Serious[b]	Serious[c]	Not serious	All plausible residual confounding would reduce the demonstrated effect	⊕⊕◯◯ Low[a, b, c]	749	762	-	749	MD 1.02 lower (1.64 lower to 0.41 lower)
Reported Anxiety 1255 (9 RCTs)	Serious[a]	Serious[d]	Serious[c]	Not serious	All plausible residual confounding would reduce the demonstrated effect	⊕⊕◯◯ Low[a, c, d]	626	629	-	626	MD 1.07 lower (1.75 lower to 0.39 lower)
Reported satisfaction 834 (6 RCTs)	Serious[a]	Serious[b]	Serious[c]	Not serious	All plausible residual confounding would reduce the demonstrated effect	⊕⊕◯◯ Low[a, b, c]	413	421	-	413	MD 1.67 higher (0.5 higher to 2.84 higher)
Dose Midazolam 891 (6 RCTs)	Serious[a]	Serious[b]	Serious[c]	Not serious	All plausible residual confounding would reduce the demonstrated effect	⊕⊕◯◯ Low[a, b, c]	453	438	-	453	MD 0.43 lower (0.88 lower to 0.02 higher)
Dose analgesics (pethidine/ fentanyl) 685 (4 RCTs)	Serious[a]	Serious[b]	Serious[c]	Not serious	All plausible residual confounding would reduce the demonstrated effect	⊕⊕◯◯ Low[a, b, c]	343	342	-	343	MD 1.41 lower (4.14 lower to 1.32 higher)
Systolic pressure (mmHg) 975 (6 RCTs)	Serious[a]	Serious[b]	Serious[c]	Not serious	All plausible residual confounding would reduce the demonstrated effect	⊕⊕◯◯ Low[a, b, c]	483	492	-	483	MD 3.1 lower (8.15 lower to 1.96 higher)
Oxygen saturation (%) 785 (4 RCTs)	Serious[a]	Serious[b]	Serious[c]	Not serious	All plausible residual confounding would reduce the demonstrated effect	⊕⊕◯◯ Low[a, b, c]	388	397	-	388	MD 0.32 higher (0.68 lower to 1.32 higher)
Heart rate (beats per minute) 975 (6 RCTs)	Serious[a]	Serious[b]	Serious[c]	Not serious	All plausible residual confounding would reduce the demonstrated effect	⊕⊕◯◯ Low[a, b, c]	483	492	-	483	MD 3.52 lower (9.49 lower to 2.45 higher)

Explanations: a. Presence of high-risk bias (performance and detection bias) in most of the studies; b. High heterogeneity; c. Different populations, methods, endoscopists, patient reported outcomes
CI, confidence interval; MD, mean difference