Guided Imagery for Non-Musculoskeletal Pain: A Systematic Review of Randomized Clinical Trials

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Abstract

Context. Our previous review of the literature concluded that there is encouraging evidence that guided imagery alleviates musculoskeletal pain, but the value of guided imagery in the management of non-musculoskeletal pain remains uncertain.

Objectives. The objective of this systematic review was to assess the effectiveness of guided imagery as a treatment option for non-musculoskeletal pain.

Methods. Six databases were searched from their inception to February 2011. Randomized clinical trials were considered if they investigated guided imagery in human patients with any type of non-musculoskeletal pain in any anatomical location and assessed pain as a primary outcome measure. Trials of motor imagery and hypnosis were excluded. The selection of studies, data extraction, and validation were performed independently by two reviewers.

Results. Fifteen randomized clinical trials met the inclusion criteria. Their methodological quality was generally poor. Eleven trials found that guided imagery led to a significant reduction of non-musculoskeletal pain. Four studies found no change in non-musculoskeletal pain with guided imagery in comparison with progressive relaxation, standard care, or no treatment.

Conclusion. The evidence that guided imagery alleviates non-musculoskeletal pain is encouraging but remains inconclusive.

Key Words
Complementary and alternative medicine, pain, systematic review, non-musculoskeletal pain

Introduction

The prevalence of non-musculoskeletal pain (N MSP) in the U.S. population in 1992–1994 was 20.4%. To the best of our knowledge, there is no standard definition of NMSP. A proposed operational definition is as follows: NMSP...
generates nociceptive stimuli from structures other than the musculoskeletal system such as the viscera, skin, cardiovascular, genitourinary, or nervous systems; it may be acute, continuous, recurrent, chronic, or postsurgical and may be located in a wide variety of anatomical regions. Harding and Yelland noted that NMSP is more likely to occur when a patient has a history of non-musculoskeletal causes, current systemic symptoms, skin problems, or deep tenderness in the abdomen. However, it is often difficult to differentiate non-musculoskeletal causes from musculoskeletal causes. Pain of musculoskeletal origin is more likely to be triggered by movement of the affected part.

Guided imagery (GI) is a widely used complementary therapy, and its use for pain management has increased over the past two decades. However, definitions of GI used in various health science disciplines are inconsistent. In this review, we define GI as follows: GI involves the generation or recall of different mental images, such as perception of objects or events, and can engage mechanisms used in cognition, memory, and emotional and motor control. The images are typically visualized within a state of relaxation, possibly with a specific outcome in mind (e.g., pain relief). Weydert et al. suggested that during GI, all the senses should be used because the more detail with which the image is sensed, the more potential for pain relief it has. GI has been suggested as an effective treatment for cancer pain. A recent systematic review concluded that the evidence of the effectiveness of GI in alleviating musculoskeletal pain (MSP) is encouraging but inconclusive. The therapeutic value of GI in the treatment of pain other than musculoskeletal and cancer pain, however, remains unclear. The rationale for this research was to continue investigations into the possible analgesic effects of GI. Therefore, the aim of this systematic review was to critically evaluate the evidence for the effectiveness of GI as a treatment for NMSP.

**Methods**

Literature searches were performed to identify all controlled clinical trials of GI for human patients with any type of NMSP. The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, AMED, and PsycINFO were searched from their inception to February 2011. A manual search was carried out using the reference lists of articles located through a scoping search in major electronic databases and through scanning our own files. Reference lists of all retrieved articles were hand-searched for relevant studies. No language restrictions were imposed.

All retrieved studies, including uncontrolled trials, case studies, and preclinical and observational studies, were reviewed for safety information. Only randomized controlled trials (RCTs) testing GI in human patients with NMSP of any duration and intensity were considered for evaluation of the effectiveness of GI. Trials of motor imagery and hypnosis were excluded. Trials also were excluded if pain was not a primary outcome measure or if the trials were related to MSP or if GI was bundled into a complex therapeutic package. However, studies of GI combined with relaxation were included in the review because relaxation is commonly used during GI to achieve a state of relaxed focus. All included articles were read in full.

Two of the authors extracted data independently using a custom-made data extraction form. For each study, trial design, randomization, blinding, dropout rate, inclusion and exclusion criteria, details of treatment method and control groups, main outcome measures, and main results were extracted. Methodological quality of studies was assessed using the 5-point Jadad score. Clinical trials scoring 3 or more points were considered high quality. Differences in scoring between reviewers were resolved through discussion. The mean change in pain ratings from baseline was considered the primary outcome measure. Changes in pain ratings were used to assess the differences between the intervention and control condition. Effect sizes were calculated for the effect of GI on pain outcome measures. Difference scores between experimental and control groups were calculated. If other statistics, such as F, t, mean, and/or standard deviations, were reported, they were converted to correlations using commonly available formulas. The difference scores were then converted to eta-squares and d statistics using Cohen’s formulas.
Results

Our search strategy generated a total of 2478 references, of which 155 were potentially relevant (Fig. 1). A total of 43 clinical trials were retrieved for further evaluation, and 15 of these, involving 1172 human patients with NMSP, were eligible for review. In all of these trials, GI was used as the only treatment or was combined with relaxation and standard care. Some studies used pleasant imagery, whereas others used pain control imagery (Table 1).

Populations of patients with NMSP were heterogeneous, with pain types ranging from postoperative pain to abdominal pain (Table 2). Eight (53.3%) of the RCTs involved adult subjects; the remainder (46.7%) involved pediatric subjects. Control groups received standard or usual care, relaxation, breathing exercises, or no intervention. Primary outcome measures included the visual analogue scale, numeric rating scale, the Facial Affective Scale, Likert scales, and the Abdominal Pain Index. The quality of the RCTs ranged from 1 to 4 points on the Jadad scale.

Eleven RCTs showed significantly greater reduction of NMSP with GI than with no intervention, standard care, or breathing exercises. Four RCTs showed no significant effect of GI over progressive relaxation, standard care, or no intervention. In seven of the 15 reviewed trials, statistics needed for effect size calculation were not reported and/or could not be derived or recreated. Effect sizes (Cohen’s d) of GI to reduce NMSP calculated in the remainder of the trials ranged from 0.05 (small) to 1.93 (large) (Table 1).

Effects of GI on Adults

Carrico et al., who explored the effects of GI on pelvic pain and urinary symptoms in women with interstitial cystitis, reported significant improvements in mean pain scores at the end of the study in the GI group. This RCT, however, lacked appropriate blinding and allocation concealment and did not use intention-to-treat analysis and power calculations. We scored this study a 3.

Daake and Gueldner examined the effectiveness of pleasant imagery in the management of acute postsurgical pain. The GI group reported significantly less postsurgical pain than a control group and consumed significantly less pain medication. This study, however, lacked appropriately described randomization, blinding, power calculations, dropouts, and intention-to-treat analysis. This study was scored a 1.

Danhauer et al. measured differences in state anxiety and perceived pain level between a GI group and a standard care group after colonoscopy and found no differences in either anxiety or pain. This study lacked appropriately described randomization, blinding, power calculations, dropouts, and intention-to-treat analysis. This study was scored a 2.

Gonzales et al. evaluated the effects of GI on postoperative outcomes in patients undergoing same-day surgical procedures. They reported significantly less pain in the GI group at two hours after surgery. However, the study did not report an appropriate sampling method or numbers of dropouts. We scored it a 3.

Haase et al. looked at whether brief psychological interventions to reduce perioperative stress improved the postoperative course of patients undergoing abdominal surgery. They reported no benefits of GI, as compared with a control group. This study lacked appropriately described randomization and sampling methods. We scored it a 4.
<table>
<thead>
<tr>
<th>First Author (year)</th>
<th>Study Design</th>
<th>Condition/Sample Size</th>
<th>Intervention</th>
<th>Control</th>
<th>Pain Measurement Methods</th>
<th>Main Result</th>
<th>Adverse Effects</th>
<th>Author’s Conclusion</th>
<th>Effect Size (Cohen’s d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ball34 (2003)</td>
<td>RCT with two groups</td>
<td>11 pediatric patients with recurrent abdominal pain</td>
<td>GI + relaxation</td>
<td>No intervention</td>
<td>FACES</td>
<td>67% decrease in pain in GI + relaxation group</td>
<td>NIP</td>
<td>GI is an effective and safe treatment for childhood RAP</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Carrico33 (2008)</td>
<td>RCT with two groups</td>
<td>30 patients with interstitial cystitis</td>
<td>GI</td>
<td>No intervention (rest)</td>
<td>VAS</td>
<td>Significant improvements in mean pain scores ($P = 0.039$)</td>
<td>NIP</td>
<td>GI may be a useful tool to offer women with interstitial cystitis for pain and symptom management</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Daake32 (1989)</td>
<td>RCT with two groups</td>
<td>32 patients with posturgical pain</td>
<td>Pleasant imagery</td>
<td>No intervention</td>
<td>VAS 100 mm</td>
<td>Significantly less posturgical pain in the GI group ($P &lt; 0.05$)</td>
<td>NIP</td>
<td>“These findings suggest that nurses can enhance the management of postoperative pain by teaching patients to use pleasant imagery.”</td>
<td>1.76</td>
</tr>
<tr>
<td>Danhauer31 (2007)</td>
<td>RCT with three groups</td>
<td>170 patients after colposcopy</td>
<td>1. Music 2. GI</td>
<td>SC</td>
<td>VAS 100 mm</td>
<td>No between-group differences</td>
<td>NIP</td>
<td>“Mind-body interventions had no statistically significant impact on reported anxiety, perceived pain, or satisfaction with care (…)”</td>
<td>0.20</td>
</tr>
<tr>
<td>Gonzales30 (2010)</td>
<td>Single-blind RCT with two groups</td>
<td>44 patients with postoperative pain</td>
<td>GI</td>
<td>No intervention</td>
<td>vVAS</td>
<td>Significantly less pain in GI group ($P = 0.041$) at two hours</td>
<td>NIP</td>
<td>“The use of guided imagery in the ambulatory surgery setting can (…) result in less postoperative pain (…)”</td>
<td>0.49 at one hour; 0.53 at two hours</td>
</tr>
<tr>
<td>Haase39 (2005)</td>
<td>Single-blind RCT with three groups</td>
<td>74 patients with posturgical pain</td>
<td>GI</td>
<td>1. Relaxation 2. No intervention</td>
<td>VAS 100 mm</td>
<td>No between-group differences</td>
<td>NIP</td>
<td>“(…) guided imagery and relaxation yielded a very positive patient response but did not show a clinically relevant influence (…)”</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Huth28 (2004)</td>
<td>RCT with two groups</td>
<td>73 pediatric patients with postoperative pain</td>
<td>GI</td>
<td>SC</td>
<td>1. Oucher Scale 2. FACES</td>
<td>Significantly lower pain in GI group</td>
<td>NIP</td>
<td>GI should be used to reduce postoperative pain</td>
<td>0.44 at one to four hours after surgery; 0.22 at 22–27 hours after discharge</td>
</tr>
</tbody>
</table>
Study after they became distressed when they listened to the tape.

Lambert (1996)

RCT with two groups
52 pediatric patients with surgical pain
GI
No intervention
NRS
Significantly lower pain ratings
NIP
Positive effects of GI on pediatric postsurgery patients
Insufficient data

Laurion (2003)

Single-blind RCT with three groups
84 patients with postoperative pain
GI
1. Music
2. SC
Verbal report on a VAS-like scale (10 cm)
No between-group differences
NIP
“(...) a decrease of analgesic requirements after surgical treatment was observed.”
Insufficient data

Omlor (2000)

RCT with two groups
208 patients with postoperative pain
GI
No intervention
VAS
Significantly less pain in the visualization group ($P < 0.05$)
NIP
“Guided imagery significantly reduces postsurgical anxiety, pain, and narcotic requirements of colorectal surgery and increases patient satisfaction.”
Insufficient data

Pederson (1995)

RCT with two groups
24 pediatric patients with cardiac catheterization
60 pediatric patients with postoperative pain
GI
No treatment
VAS 100 mm
No changes in pain scores
NIP
GI may assist in coping with anxiety
Insufficient data

Pökkö (2008)

RCT with two groups
60 pediatric patients with postoperative pain
GI
SC
VAS
Significantly less pain in GI group
NIP
GI can reduce postoperative pain
0.43 immediately after surgery; 0.05 at one hour postintervention
1.93

Tusek (1997)

RCT with two groups
130 patients with postoperative pain
GI + SC
SC
VAS 100 mm
Significantly less pain in the GI group ($P < 0.001$)
NIP
“Guided imagery significantly reduces postsurgical anxiety, pain, and narcotic requirements of colorectal surgery and increases patient satisfaction.”
Insufficient data

van Tilburg (2009)

RCT with two groups
34 pediatric patients with functional abdominal pain
GI
SC
API (two questions)
Significant improvement in abdominal pain
NIP
Gi + SC was superior to SC only
Insufficient data

Weidert (2006)

RCT with two groups
22 pediatric patients with RAP
GI
Breathing exercises
FACES
Significantly greater decrease in the number of days with pain
None occurred
GI has the potential to benefit children with RAP
0.37

RCT = randomized controlled trial; GI = guided imagery; FACES = Facial Affective Scale; NIP = no information provided; RAP = recurrent abdominal pain; VAS = visual analogue scale; SC = standard care; vVAS = vertical visual analogue scale; NRS = numeric rating scale; API = Abdominal Pain Index.
Laurion and Fetzer\textsuperscript{26} examined the effects of GI or music therapy on postoperative pain, nausea and vomiting, and length of stay for gynecologic laparoscopic patients. They reported significantly less pain at discharge in both GI and music therapy groups than in controls. This study, however, lacked appropriately described randomization, an appropriate sampling method, power calculations, and intention-to-treat analysis. This study was scored a 1.

Omlor et al.\textsuperscript{35} evaluated the influence of preoperative GI on postoperative pain in adults. They reported significantly less pain and analgesic use in the GI group than in the control group. However, several secondary outcome measures, including postoperative nausea, infections, and fever, showed no significant differences. This RCT lacked appropriately described eligibility criteria, randomization, blinding, allocation concealment, dropout rate, and intention-to-treat analysis. We scored this study a 1.

Tusek et al.\textsuperscript{23} looked at whether GI used in the perioperative period improved the outcomes of

\begin{table}[h]
\centering
\caption{Details of GI Intervention\label{tab:gi_intervention}}
\begin{tabular}{ll}
\hline
First Author (Year) & GI Intervention (quote) \\
\hline
Ball\textsuperscript{34} (2003) & “…learning to feel the difference between tense and relaxed muscles and using your imagination to tell your body what to do.”

Carriço\textsuperscript{55} (2008) & “One group (treatment) listened to a 25-minute guided imagery compact disc (CD), that was created specifically for women with pelvic pain and IC, twice a day for 8 weeks. […] you may begin to feel healing warmth melt into your bladder … coating the inside and outer surfaces … letting each and every cell relax and release its tension … soothing any painful areas with its gentle golden glow.”

Daake\textsuperscript{32} (1989) & Professionally prepared tape recordings of three preselected scenes (a beach scene, a mountain cabin scene, and an autumn scene) were made available to each patient in the experimental group for practice throughout the day and evening prior to surgery. The scenes were designed to engender the use of all five senses. Patients in the imagery group were also encouraged to use their own pleasant past experiences to form an image. Each individual in the treatment group was instructed to use the imagery technique three times per day after surgery (upon first waking, midafternoon, and evening), for a period of 15 to 20 minutes each time.”

Danhauer\textsuperscript{31} (2007) & “Participants in the imagery group listened to a 20-minute audio recording entitled A Meditation to Help You Be Relaxed and Awake During Medical Procedures by Naparstek (www.healthjourneys.com).”

Gonzalez\textsuperscript{30} (2010) & “This CD led the patient through a progressive relaxation and guided imagery exercise. (…) This CD consisted of soothing biorhythmic music combined with positive, encouraging statements.” [28 minutes]

Haase\textsuperscript{29} (2005) & “The guided imagery tape taught patients to become calm and activate their inner resources. Patients were sent on an imaginative journey to a special place where they could feel safe, comforted, and supported. They were encouraged to confront and work through feelings of anxiety and stress.” [12 minutes]

Huth\textsuperscript{30} (2004) & “The videotape presentation (deep breathing and imagery techniques), audiotape (deep breathing, muscle relaxation, music, and suggestions for picturing a park), and booklets were given to the child and parent at home 2–22 days prior to the scheduled surgery to teach the child imagery skills for postoperative pain.”

Lambert\textsuperscript{27} (1996) & “Each child was asked to select an enjoyable image that felt good. Each child’s image was incorporated into an individually tailored relaxation exercise. During the imagery practice, the investigator guided the child through a rehearsal of the impending surgical experience and included suggestions for healing, uncomplicated recovery, and minimal pain.”

Laurion\textsuperscript{26} (2003) & “Tape I, side A, contains imagery geared for preparing patients for surgery. Tape I, side B, consists of 10 minutes of positive affirmations that can be used to prepare for surgery but are also used for healing after surgery. Tape II, which consists of the musical score from tape I, was played continuously on an auto-reverse Walkman during the patient’s surgery (…)”

Omlor\textsuperscript{35} (2000) & “Patients received preoperatively under supervision of a psychologist a visualization therapy in connection with 45 min relaxation exercises.”

Pederson\textsuperscript{25} (1995) & “Based on the child’s previously identified favorite activities and places, the intervener guided the child’s imagery of going to the child’s favorite places and doing his or her favorite activities (Kuttner, 1986). While guiding the child’s imagery the intervener asked the child to notice the sights and sounds in the child’s favorite place, or how it felt to perform favorite activities (…).” “The intervener also provided suggestions of feeling comfortable, competent, safe, and happy.”

Pälkiä\textsuperscript{24} (2008) & “… allowed scope for the child’s own pleasant imagery, reassurance and repeatable music with sounds of nature provided possibilities to achieve a deep state of relaxation…” “…the child was encouraged to mentally choose a favorite place (…)”, and “…proceeded toward this place along a comfortable path (downward).” At the end of the trip, the child returned along this path (upward).”

Tusek\textsuperscript{23} (1997) & “The guided imagery tape taught techniques that allowed them to become calm and focused. They were then brought to a ‘special place’ in their mind that was safe, secure, protected, supported, and relaxed. The imagery story provided patients to confront and work through any feelings of fear, anxiety, and negativity. Patients were instructed to listen to the tape without interruption twice per day, once in the morning and once in the evening. Tapes were 20 minutes long and had a soft, soothing, musical background.” [3 days before, during, and after surgery]

van Tilburg\textsuperscript{22} (2009) & “Each session includes induction imagery to produce relaxation, followed by imagery and suggestions for decreased discomfort and healing.”

Weyerd\textsuperscript{36} (2006) & “Once achieving relaxation, subjects were asked to invite an image to come to mind that represented their pain. They were encouraged to describe the image in detail using all the senses as the more detailed the image is sensed, the more potential the pain reliever it could be. Once this image was established, they were then asked to invite a second image to come that would get rid of the pain (first image).”

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\end{tabular}
\end{table}
Colorectal surgery patients. They reported significantly less pain and opioid use in the GI group than in the control group, but the study lacked blinding, dropout rate, and intention-to-treat analysis. This study was scored a 2.

Effects of GI on Pediatric Patients
Ball et al.34 investigated the use of relaxation and GI for children suffering from recurrent abdominal pain. They found that the children experienced a 67% decrease in pain during the therapy. This RCT, however, lacked appropriately described eligibility criteria, randomization, blinding, allocation concealment, dropout rate, and intention-to-treat analysis. We scored this study a 1.

Huth et al.28 investigated the effectiveness of imagery, in addition to routine analgesics, in reducing tonsillectomy and adenoidectomy pain and anxiety after ambulatory surgery and at home. They found that by controlling for trait anxiety and analgesic intake one to four hours before the pain measures, the analyses showed significantly less pain in the treatment group one to four hours after surgery. This study, however, lacked appropriate sampling methods, blinding, formal power and sample size calculations, and intention-to-treat analysis. We scored this study a 3.

Lambert27 examined the effects of hypnosis/GI on the postoperative course of pediatric surgical patients. Significantly lower postoperative pain ratings and shorter hospital stays were reported in the hypnosis/GI group. Yet, this study lacked appropriate sampling methods, explicit eligibility criteria, appropriately described randomization, blinding, dropout rate, power calculations, and intention-to-treat analysis. This study was scored a 1.

Pederson25 examined the effects of imagery on children’s pain and anxiety during cardiac catheterization. No significant differences in pain were reported between groups. This RCT lacked fully described randomization, blinding, power and sample size calculations, exclusion criteria, loss-to-follow-up ratio, and intention-to-treat analysis. We scored this study a 1.

Pölkki et al.33 examined the efficacy of imagery and relaxation for postoperative pain relief in hospitalized children. They reported that the children in the experimental group had significantly less postoperative pain than the control children. This RCT lacked sufficiently described randomization, concealed allocation, clearly described eligibility criteria, power calculations, loss to follow-up rate, and intention-to-treat analysis. It was scored a 1.

van Tilburg et al.22 developed and assessed a home-based, GI treatment protocol for children with functional abdominal pain. They reported significant improvements in abdominal pain in the GI group. However, this study lacked blinding and had a small sample. We scored this study a 3.

Finally, Weydert et al.5 compared the efficacy of GI and breathing exercises alone in the treatment of recurrent abdominal pain in children. They reported that children who learned GI with muscle relaxation had significantly fewer days with pain than those who learned breathing exercises alone after one and two months. This study had a small sample size, however, and lacked therapist blinding. We scored this study a 4.

Discussion
In a previous review that focused on GI for MSP, we included nine RCTs and concluded that “the evidence that GI alleviates MSP is encouraging but not conclusive.”7 The present review evaluated the evidence for the effectiveness of GI as a treatment for NMSP. Fifteen RCTs met our eligibility criteria. Eleven of these (73.3%) suggested that GI is effective for NMSP, and four (26.7%) showed no significantly greater effects on NMSP than progressive relaxation,29 standard care,31 or no treatment.25,26 The evidence from RCTs of GI for treating NMSP is thus encouraging but inconclusive. There are several reasons for this. The patients who received GI were heterogeneous in terms of clinical condition treated. There also was heterogeneity in design and methods including types of GI, use of control vs. attention control groups, exclusion and inclusion criteria, and primary pain outcome measures. Given such variability in GI intervention and control groups, it is difficult to draw any definite conclusions.

In most studies included in the present review, methodological quality was low, with only six of 15 trials scoring 3 or more out of a possible 5 points on the Jadad scale for methodological quality (Table 3).5,22,28—30,33 Of these high-quality trials, five of six favored GI,5,22,28,30,33
but one showed no significant effect over relaxation.29 Five of nine low-quality trials (less than 3 on the Jadad score) reported a significant reduction in NMSP after the GI intervention, and four low-quality RCTs reported no change in pain scores.

Guidelines for designing and reporting RCTs note that descriptions of adverse effects are an ethical imperative in clinical research.36 Our review suggests that in GI research, this imperative is frequently ignored. Two of the 15 RCTs reviewed reported adverse events,5,28 but 13 failed to provide that information (Table 1).22–27,29–34

Our review had several limitations. We attempted to identify all RCTs on the subject, but it is conceivable that some negative RCTs remain unpublished, distorting the overall picture. Other limitations of our review include the poor quality of the primary data, poor reporting of results, and lack of statistical pooling as a result of the high heterogeneity of the studies. Also, difficulties with conceptualization of NMSP may have affected the findings of the review. Finally, the total number of trials included in our review and the total numbers in samples prevent any definitive judgments.

To definitively establish the effects of GI on pain in NMSP patients, adequately designed trials are needed. Studies of GI need to follow the standards of trial design and reporting as per the Consolidated Standards of Reporting Trials. More specifically, studies need to have adequate samples based on power calculations, use validated outcome measures, control for nonspecific effects, and minimize other sources of bias related to internal validity. Furthermore, GI interventions should be standardized. Although we assessed outcome measures related only to pain, other outcomes such as analgesic consumption, anxiety, depression, disability, function, length of hospital stay, or quality of life should be taken into account in future research. Finally, the inclusion of biobehavioral mediating variables can lead to greater understanding of the mechanisms by which GI produces its effects. In addition to psychological mediators, such as improved pain self-efficacy,33 possible modes of action of GI may include modulation of immune and nervous system through the release of enkephalins, endorphins, cholecystokinin, and dopamine and/or the inhibition of prostaglandin and cortisol.37,38

In conclusion, the evidence that GI alleviated NMSP overall is positive, but no definite judgments can be made. Further rigorous research seems warranted.

Disclosures and Acknowledgments

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References


