GEMs
GOOD EVIDENCE MATTERS

# GEMs of the Week

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Family Physicians Inquiries Network

## What's in this week's issue?

**Week of March 25 - 29, 2024**

**SPOTLIGHT: Evaluation of Probiotics for the Treatment of Irritable Bowel Syndrome**

# Evaluation of Probiotics for the Treatment of Irritable Bowel Syndrome

**Efficacy of Probiotics for Irritable Bowel Syndrome: A Systematic Review and Network Meta-Analysis**

Zhang T, Zhang C, Zhang J, Sun F, Duan L. Efficacy of Probiotics for Irritable Bowel Syndrome: A Systematic Review and Network Meta-Analysis. *Front Cell Infect Microbiol.* 2022;12:859967. Published 2022 Apr 1. doi:10.3389/fcimb.2022.859967



**KEY TAKEAWAY:** *Bacillus coagulans* is effective at improving IBS-related symptoms.

**STUDY DESIGN:** Systematic review and network meta-analysis of 43 randomized control trials (RTC) (N=5,531)

**LEVEL OF EVIDENCE:** STEP 1

**BRIEF BACKGROUND INFORMATION:** Irritable bowel syndrome (IBS) is a common and chronic medical condition characterized by gastrointestinal (GI) distress (pain, bloating, and change in bowel habits) that can affect patients' quality of life. The efficacy of different probiotic species has not been studied. This study aims to compare the different probiotic species for the treatment of IBS-related symptoms to identify the best intervention.

**PATIENTS:** Patients with established IBS diagnosis

**INTERVENTION:** Administered different probiotic species

**CONTROL:** Administered placebo

**PRIMARY OUTCOME:** Efficacy of different probiotic species on symptom relief scores, global symptoms, abdominal pain, bloating, straining, quality of life, and adverse events

Secondary Outcome: Effect of different probiotic species on quality of life

**METHODS (BRIEF DESCRIPTION):**

- Systematic search of databases including PubMed, Cochrane Library, Web of Science, and Medline.
- Eligible criteria included:
  - RTCs that compared the efficacy and tolerability of probiotics for patients with irritable bowel syndrome.
  - Patients had an established diagnosis of IBS based on the Rome criteria.
  - Clear probiotic speciation could be identified and included: *S. boulardii, S. cerevisiae, E. coli, B. bifidum, B. coagulans, L. acidophilus, LGG, L. paracasei, L. salivarius, L. plantarum, B. longum, L. casei, L. gasseri, B. infantis, C. butyricum, L. reuteri* and *B. lactis*.
  - Probiotic dosage and duration could be identified.
  - Patients were required to have a follow-up of at least one week.
- Data evaluated included subtypes of IBS and treatment details (probiotic type, probiotic dosage, response rate to treatment/placebo, duration of treatment, and outcome measure).
  - Symptom relief was calculated statistically from individual RTC response rate (percent improvement) to network plot analysis.
- Network meta-analysis was performed with Stata software. Odds ratios with confidence intervals calculated categorical and continuous data.
- Network heterogeneity was determined using $I^2$ statistics.
- The probabilities of the surface under the cumulative ranking curve (SUCRA) between all primary and secondary outcomes were calculated.
- Meta-regression analysis was conducted to explore whether the lengths and doses of interventions were associated with efficacy and adverse events.

**INTERVENTION (# IN THE GROUP):** Not available

**COMPARISON (# IN THE GROUP):** Not available

**FOLLOW-UP PERIOD:** At least one week

**RESULTS:**

Primary Outcome –

- Different probiotic species improved the following compared to placebo:
  - Symptom relief rate:
    - *B. coagulans* (odds ratio [OR] 61; 95% CI, 15–249)
    - *L. plantarum* (OR 16; 95% CI, 2.9–84)
    - *L. acidophilus* (OR 3.0; 95% CI, 1.0–8.7)
    - SUCRA analysis showed that *B. coagulans* ranked best amongst treatment interventions.
  - Global symptoms:
    - *B. coagulans* (standard mean difference [SMD] –2.0; 95% CI, –2.4 to –1.6)
    - *B. infantis* (SMD –0.74; 95% CI, –1.5 to –0.01)

        - SUCRA analysis showed that *B. coagulans, C. butyricum*, and *B. longum range* in the top three interventions for improving global symptoms.
    - Abdominal pain:
        - *B. coagulans* (SMD –1.7; 95% CI, –2.2 to –1.3)
        - *S. cerevisiae* (SMD –0.54; 95% CI, –1.1 to 0.00)
        - SUCRA analysis showed that *B. coagulans* ranked best amongst treatment interventions.
    - Bloating:
        - *B. coagulans* (SMD –1.4; 95% CI, –1.9 to –0.95)
        - SUCRA analysis showed that *B. coagulans* ranked best amongst treatment interventions.
    - Straining:
        - *B. coagulans* (SMD –1.3; 95% CI, –1.6 to –0.94)
        - SUCRA analysis showed that *B. coagulans* ranked best amongst treatment interventions.

Secondary Outcome –

- No probiotic is better than administered placebo in improving the quality of life of patients with IBS.

**LIMITATIONS:**

- Self-reported symptoms introduce reporting bias.
- A lack of available trials and a lack of large sample sizes for direct comparison may influence results.
- Due to limited data, authors were unable to evaluate other clinical indicators (bowel habits, stool consistency, gut motility, inflammatory-related factors, gut microbiome) that may affect outcomes.
- Methodologies of the included randomized control trial varied (design, population, criteria, IBS subtypes, etc.) making it difficult to draw robust conclusions.

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# Ketorolac: How Much is Enough for Acute Pain?

**Comparative Effectiveness of Ketorolac Dosing Strategies for Emergency Department Patients with Acute Pain**

Forestell B, Sabbineni M, Sharif S, Chao J, Eltorki M. Comparative Effectiveness of Ketorolac Dosing Strategies for Emergency Department Patients with Acute Pain. *Ann Emerg Med.* 2023;82(5):615-623. doi:10.1016/j.annemergmed.2023.04.011



**KEY TAKEAWAY:** Parenteral ketorolac given at doses of 10–20 mg is as effective at controlling acute pain as doses of 30 mg or more.

**STUDY DESIGN:** Systematic review of five randomized controlled trials (RCTs) (N=629)

**LEVEL OF EVIDENCE:** STEP 2 (downgraded due to the small number of studies reviewed)

**BRIEF BACKGROUND INFORMATION:** To reduce opioid use, NSAIDs are frequently prescribed as a pain control alternative. However, NSAIDs have a maximum dose beyond which further pain improvement will not occur and are associated with significant side effects. Given its parenteral availability, ketorolac is frequently given for acute pain but often at doses beyond its analgesic ceiling. This systematic review examines the effectiveness and safety of different ketorolac dosing for the relief of acute pain.

**PATIENTS:** Adults in the emergency department for acute pain

**INTERVENTION:** Low dose parenteral ketorolac

**CONTROL:** High dose parenteral ketorolac

**PRIMARY OUTCOME:** Pain rating, adverse events, need for rescue analgesia

**METHODS (BRIEF DESCRIPTION):**

- A systematic search of online databases including RCTs comparing different doses of ketorolac in the management of acute pain was performed.
- Ketorolac doses of <30 mg were considered a low dose and ≥30 mg was a high dose.
- Inclusion criteria included studies that reported pain scores, the need for rescue analgesia, and adverse events.
- Studies of patients with cancer-related, chronic, and perioperative pain were excluded.
- Pain scales were converted to a 100 mm visual analog scale (VAS); higher scores indicate greater pain intensity.
- The 60-minute endpoint, or the latest reported endpoint post-drug administration was used.
- Overall certainty for each outcome was assessed.

**INTERVENTION (# IN THE GROUP):** 386

**COMPARISON (# IN THE GROUP):** 243

**FOLLOW-UP PERIOD:** 1–12 hours; pain scores were reported up to two hours post-drug administration

**RESULTS:**

Primary Outcome –

- Low-dose ketorolac had no impact on pain scores compared to high-dose ketorolac (VAS mean difference [MD] 0.05 mm; 95% CI, –4.9 to 5.0; moderate certainty).
- A ketorolac dose at 10 mg likely had no impact on pain scores compared to a high dose of ketorolac (VAS MD 1.6 mm; 95% CI, –8.9 to 5.7; low certainty).
- Low-dose ketorolac did not affect rates of adverse events compared to high-dose ketorolac (relative risk [RR] 0.84; 95% CI, 0.54–1.3; low certainty).
- Low-dose ketorolac may increase the need for rescue analgesia (RR 1.3; 95% CI, 0.86–1.9; low certainty).

**LIMITATIONS:**

- Only five RCTs were included in the systematic review.
- Patients at higher risk of NSAID-related adverse events were not included, so results may not be applicable.
- Low to moderate level of certainty of the outcomes.

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*The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense.*

# Neuropathic Pain: Can Topical Clonidine Provide More Relief than Placebo?

**Topical Clonidine for Neuropathic Pain in Adults**

Serednicki WT, Wrzosek A, Woron J, et al. Topical clonidine for neuropathic pain in adults. *Cochrane Database Syst Rev*. 2022;5(5):CD010967. Published 2022 May 19. doi:10.1002/14651858.CD010967.pub3



**KEY TAKEAWAY:** Topical clonidine (TC) can provide moderate pain relief in adults with painful diabetic neuropathy (PDN) compared to placebo. However, TC does not yield substantial pain reduction in adults with PDN.

**STUDY DESIGN:** Systemic review of four randomized controlled trials (RCTs) (N=743)

**LEVEL OF EVIDENCE:** STEP 2 (downgraded due to low quality of evidence)

**BRIEF BACKGROUND INFORMATION:** As the prevalence of neuropathic pain is increasing, it can be challenging to manage. Clonidine, originally used to treat hypertension, has demonstrated effectiveness in treating acute and chronic pain, although systemic use comes with unfavorable side effects. In recent years, there has been a shift among providers toward the topical application of clonidine for neuropathic pain. However, there remains a scarcity of evidence on the efficacy and safety of topical clonidine for neuropathic pain in adults.

**PATIENTS:** Adults with PDN

**INTERVENTION:** TC gel

**CONTROL:** Topical placebo or capsaicin

**PRIMARY OUTCOME:** Pain reduction

Secondary Outcome: Withdrawals due to adverse effects, presence of at least one adverse event, withdrawal due to lack of efficacy, change in average pain intensity

**METHODS (BRIEF DESCRIPTION):**

- A comprehensive literature search of double-blinded RCTs with at least two weeks of treatment was performed.
- Adults who were ≥18 years old with one or more chronic neuropathic pain conditions were included in this study.
- The intervention group received 0.1% or 0.2% TC which was applied to the painful area two or three times daily.
- The control group received a topical placebo or capsaicin which was applied to the painful area two or three times daily.
- Pain was measured using the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) or Patient Global Impression of Change (PGIC) scale.
    - IMMPACT scale measured moderate relief (pain relief of at least 30%) and substantial relief (pain relief of at least 50%) compared to baseline.
    - PGIC was a 7-point scale from very much worse (=1) to very much improved (=7).

**INTERVENTION (# IN THE GROUP):** 399

**COMPARISON (# IN THE GROUP):** 347

**FOLLOW-UP PERIOD:** 8–12 weeks

**RESULTS:**

Primary Outcome –

- TC did not result in more patients with a substantial pain reduction within 12 weeks compared to placebo or capsaicin.
    - TC vs placebo (1 RCT, n=179; risk ratio [RR] 1.2; 95% CI, 0.78–1.9)
    - TC vs capsaicin (1 RCT, n=139; RR 1.4; 95% CI, 0.99–2.0)
- TC resulted in more patients with a moderate pain reduction within 8–12 weeks compared to placebo (2 RCTs, n=344; RR 1.4; 95% CI, 1.0–1.8; $I^2$=0%).
- TC did not improve pain (PGIC scale) within 12 weeks compared to placebo (1 RCT, n=179; RR 1.1; 95% CI, 0.76–1.5).

Secondary Outcome –

- In both TC vs placebo and TC vs capsaicin, there were no significant differences in the following between the two groups:
    - Withdrawals due to adverse effects
    - Presence of at least one adverse event
    - Withdrawal due to lack of efficacy
    - Change in average pain intensity

**LIMITATIONS:**

- Some studies included were low-quality trials, such as unpublished data.
- The treatment period of the studies was relatively short from 8–12 weeks. Longer duration trials would

be more appropriate to establish the efficacy of TC for pain.

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*The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Air Force Medical Department, the Air Force at large, or the Department of Defense.*

# RSV Vaccine Effective in Older Adults

**Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults**

Papi A, Ison MG, Langley JM, et al. Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults. *N Engl J Med.* 2023;388(7):595-608.
doi:10.1056/NEJMoa2209604



**KEY TAKEAWAY:** Single dose respiratory syncytial virus (RSV) vaccine was effective in older adults in preventing infection with RSV, as well as morbidity and mortality from RSV-related lower and upper respiratory tract disease.

**STUDY DESIGN:** Randomized, single-blind, controlled trial

**LEVEL OF EVIDENCE:** STEP 3 (downgraded due to researchers not blinded to intervention, homogenous patient population, low incidence of disease)

**BRIEF BACKGROUND INFORMATION:** RSV is a key contributor to both adult and child acute upper and lower respiratory tract infections with resultant morbidity and mortality. At the time the article was published there was no approved vaccine against RSV infection. This study analyzed the efficacy of the novel RSV vaccine in older adults to prevent RSV-related lower respiratory tract disease.

**PATIENTS:** Older adults

**INTERVENTION:** RSV vaccine

**CONTROL:** Placebo vaccine

**PRIMARY OUTCOME:** Prevention of RSV-related lower respiratory tract disease

Secondary Outcome: Prevention of severe disease, RSV-related acute upper respiratory infection (URI), infection from RSV subtype A and B, adverse events

**METHODS (BRIEF DESCRIPTION):**

- Adults aged ≥60 years old across five continents were included. Chronic medical conditions were allowed if the patient was considered medically stable.
- Results were from the first RSV season in the northern hemisphere.
- Patients were blinded and randomized to either:
  - 0.5 mL of RSV vaccine
  - Matching dosage saline placebo
- Participants were blinded to treatment, however the researchers were not.
- Efficacy was measured by monitoring self-reported URI symptoms by participants followed by testing from RSV subtypes A and B.
- Patients were contacted at two-week intervals to asses for mild respiratory symptoms (congestion, rhinorrhea, mild cough, etc.) not spontaneously reported.

**INTERVENTION (# IN THE GROUP):** 12,467

**COMPARISON (# IN THE GROUP):** 12,499

**FOLLOW-UP PERIOD:** 10 months after vaccination

**RESULTS:**

Primary Outcome –

- Single-dose RSV vaccination was more effective than placebo against RSV-related lower respiratory disease (83% efficacy; 96.95% CI, 58–94).

Secondary Outcome –

- Single-dose RSV vaccination was more effective than placebo against severe RSV-related disease (95% efficacy; 95% CI, 62–99).
- Single-dose RSV vaccination was more effective than placebo against RSV-related acute URI (72% efficacy; 95% CI, 56–82).
- RSV vaccination was equally effective in preventing infection from RSV subtypes A and B.
- There was no increase in adverse events in those who received RSV vaccine vs placebo.

**LIMITATIONS:**

- The patient population was homogenous with an underrepresentation of African American, Asian, and Hispanic patients.
- The patient population only represented elderly adults.
- There was a low incidence of disease in the study population.

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# Does My Child Need Tympanostomy Tubes Placed?

**Tympanostomy Tubes or Medical Management for Recurrent Acute Otitis Media**

Hoberman A, Preciado D, Paradise JL, et al. Tympanostomy Tubes or Medical Management for Recurrent Acute Otitis Media [published correction appears in N Engl J Med. 2022 May 12;386(19):1868*]. N Engl J Med.* 2021;384(19):1789-1799. doi:10.1056/NEJMoa2027278



**KEY TAKEAWAY:** Tympanostomy tube placement as a treatment option for recurrent acute otitis media (AOM) in immunized children 6–35 months old, compared to medical management, does not change the rate of subsequent episodes of infection requiring antibiotics during a two-year follow-up period.

**STUDY DESIGN:** Randomized controlled trial

**LEVEL OF EVIDENCE:** STEP 3 (downgraded due to nonblinded treatment)

**BRIEF BACKGROUND INFORMATION:** Tympanostomy tube placement is frequently performed in the pediatric population, although current guidelines and official recommendations remain inconsistent. In addition, most of the previous trials on recurrent AOM are conducted before the introduction of routine pneumococcal vaccination.

**PATIENTS:** Children with a history of recurrent AOM

**INTERVENTION:** Tympanostomy tube placement

**CONTROL:** Nonsurgical antimicrobial medical management

**PRIMARY OUTCOME:** Number of AOM episodes

Secondary Outcome: Median time to the first episode of AOM, % of children who had treatment failure, number of days per year with otitis-related symptoms other than tube otorrhea, number of days of systemic antibiotic treatment, number of days per year with tube otorrhea, % of episodes categorized as probably severe, frequency distribution of episodes of AOM, % of children who had diarrhea or medication-related diaper dermatitis, the extent of antimicrobial resistance among isolated pathogens, the effect of children's illness on parents, children's quality of life.

**METHODS (BRIEF DESCRIPTION):**

- Participants: Children 6–35 months old, 36% female, and 56% White.
- Inclusion criteria: Immunized with conjugated pneumococcal vaccine meeting specified criteria for recurrent AOM, who developed acute symptoms and either middle-ear effusion with specified combinations of otalgia, tympanic membrane bulging, and tympanic membrane erythema or purulent otorrhea after enrollment.
- Patients were randomized to one of the following treatments:
  - The medical management group was treated with amoxicillin 90 mg/clavulanate 6.4 mg per kilogram of body weight per day for 10 days.
    - In the presence of a subtherapeutic response, ceftriaxone 75 mg/kg was given intramuscularly, repeated in 48 hours.
  - Tympanostomy tube placement was performed within two weeks.
    - The occurrence of otorrhea with a combination of at least one AOM symptom was treated with five drops of 0.3% of ofloxacin topically twice a day (BID) for 10 days.
    - When otorrhea persisted for more than seven days, amoxicillin-clavulanate 90 mg/6.4 mg per kilogram of body weight per day for 10 days was given.
    - Tubes extruded within six months were replaced if the child had two or more episodes of AOM within three months.
    - After six months, tubes were replaced if symptoms met the criteria for recurrent otitis media.
- The number of AOM episodes was measured using parent reports on the five-item Acute Otitis Media Severity of Symptom (AOM-SOS) scale version 4.0, with scores ranging from 0–10 with higher scores indicating greater severity.
  - For episodes managed by non-trial clinicians, documentation of one acute symptom from AOM-SOS was required, along with either membrane bulging or purulent otorrhea.
  - The illness span counted as two constituting episodes of AOM if symptoms or signs persisted

for or recured at least 17 days after starting antibiotics.

- When episodes occurred, a nasopharyngeal specimen (or throat swab in children older than 24 months) was obtained for culture to assess antimicrobial resistance.

**INTERVENTION (# IN THE GROUP):** 129

**COMPARISON (# IN THE GROUP):** 121

**FOLLOW-UP PERIOD:** Two years

**RESULTS:**

Primary Outcome –

- There was no significant difference in the number of AOM episodes per child-year between the tympanostomy and medical management group during the two-year follow-up period (1.5 vs 1.6, respectively; mean difference [MD] 0.97; 95% CI, 0.84–1.1).

Secondary Outcome –

- The median time to a first occurrence of AOM was significantly longer in the tympanostomy group compared to the control group (4.3 months vs 2.3 months, respectively; hazard ratio [HR] 0.58; 95% CI, 0.52–0.90).
- A significantly smaller percentage of children in the tympanostomy group met the criteria for treatment failure (45% vs 62%, respectively; risk ratio [RR] 0.73; 95% CI, 0.58–0.92).
- The tympanostomy group had fewer days per year with otitis-related symptoms other than tube otorrhea (mean 2.0±0.29 days vs 8.3±0.59 days; P not provided).
- The tympanostomy group received fewer days of systemic antibiotic treatment (mean 8.8±0.94 vs 13±0.90 days; P not provided).
- The tympanostomy group had more days per year with tube otorrhea (mean 8.0±1.1 days vs 2.8±0.78 days; P not provided).
- There were no significant differences in the following between the two groups:
  - Percentages of episodes categorized as probably severe
  - The frequency of distribution of episodes of acute otitis media
  - Children who had diarrhea or medication-related diaper dermatitis
  - The extent of antimicrobial resistance among isolated pathogens
  - The effect of children's illness on parents
  - Measure of the children's quality of life

**LIMITATIONS:**

- Impossibility of blinding; assignments revealed after enrollment.
- About half of the children assigned to the medical management group underwent tympanostomy tube placement secondary to treatment failure or per parental request, creating crossover bias affecting randomization.
- No language acquisition and hearing assessments were done besides parental questions on speech and hearing impairment in the OM-6 survey.
- Conductive hearing loss as a potential outcome was not implemented.

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