In adults using antibiotics, do high-dose probiotics result in greater reduction of gastrointestinal symptoms than low-dose probiotics?

**EVIDENCE-BASED ANSWER**

Compared with low-dose probiotics, high-dose probiotics reduce duration of antibiotic-associated diarrhea (AAD) and certain gastrointestinal (GI) side effects associated with antibiotic use, such as fever, abdominal pain, bloating, abdominal distension, loose stools, and constipation (SOR: B, RCTs). High-dose probiotics may also reduce incidence of AAD and *Clostridium difficile*–associated diarrhea (CDAD) (SOR: B, conflicting RCTs). Data may be biased due to industry sponsorship of trials.

A 2014 single-center, triple-blind, industry-sponsored, RCT in China evaluated the effect of probiotics on GI symptoms in 503 hospitalized adults 30 to 70 years old taking antibiotics (penicillins, cephalosporins, or clindamycin) for 3 to 14 days.¹ Exclusion criteria included pregnancy, breastfeeding, active diarrhea, prior consumption of probiotics or fermented milk products, prior probiotic allergy, uncontrolled intestinal disease, *C. difficile* infection within the past 3 months, parenteral nutrition, NPO status, immunosuppressed state, antibiotic use within the past month, and lactose intolerance. Participants were stratified by age, sex, and duration of antibiotic therapy and then randomized to receive HOWARU® Restore 4-strain probiotic formula at a high dose of 17 billion CFU (n=168), a low dose of 4.17 billion CFU (n=168), or placebo (n=167). Probiotics were initiated within 36 hours of antibiotic initiation and continued until 7 days after antibiotic completion. Compliance and GI symptoms were followed during admission and for 4 weeks after discharge.

Compared with the low-dose probiotic group, the high-dose probiotic group had a nonsignificant reduction in incidence of AAD (19.6% vs 12.5%; *P*=.08), shorter duration of AAD (3.5 days vs 2.6 days; *P*=.03) and lower incidence of fever, abdominal pain, and bloating. Incidence of CDAD was not different in the low- and high-dose groups. No adverse effects were attributed to probiotics.¹

A 2010 single-center, triple-blind, industry-sponsored RCT in China evaluated the effect of probiotics on GI symptoms in 255 hospitalized adults aged 50 to 70 years taking antibiotics (penicillins, cephalosporins, or clindamycin) for 3 to 14 days.² Exclusion criteria included use of other probiotics, active diarrhea, uncontrolled intestinal disease, documented *C. difficile* infection within the past 3 months, immunosuppressive therapy, antibiotic use within the past 30 days, or active participation in another clinical study. Participants were stratified by age and duration of antibiotic therapy and then randomized to receive Bio-K + International brand® 3-strain probiotic formula at a high dose of 100 billion CFU (n=86), a low dose of 50 billion CFU (n=85), or placebo (n=84). Probiotics were initiated within 36 hours of antibiotic initiation and continued until 5 days after antibiotic completion. GI symptoms were followed during admission and for 3 weeks after discharge. Compared with the low-dose probiotic group, the high-dose probiotic group had lower incidence of AAD (28.2% vs 15.5%; *P*=.02), shorter mean duration of AAD (4.1 days vs 2.8 days; *P*=.04), lower incidence of CDAD (9.4% vs 1.2%; *P*=.04), and lower incidence of abdominal pain, abdominal distension, loose stools, and constipation. No adverse effects were attributed to probiotic use.²

Richa Garg, MD, MS
Pooja Saigal, MD
University of Chicago
Chicago, IL


Is capsaicin cream safe and effective at reducing knee osteoarthritis pain?

**EVIDENCE-BASED ANSWER**

Capsaicin cream and its cis-isomer, cismid, have small to moderate effects reducing osteoarthritis knee pain after at least four weeks of use. Capsaicin cream is safe, but commonly causes application-site burning that rarely leads to stopping treatment (SOR: A, systematic review of RCTs and one crossover study).

A 2014 systematic review examined capsaicin cream for knee osteoarthritis in 5 double-blind RCTs and 1 case-crossover trial.
including 1,162 patients with average ages 49 to 65 years.¹ Trials assessed treatment efficacy versus placebo over 4 weeks, with 2 studies reporting data beyond 4 weeks. Capsaicin concentrations ranged from 0.025% to 0.075% used topically 3 to 4 times per day. Results were consistent across the trials with no heterogeneity. Two trials reported continued effectiveness up to 20 weeks (numerical results not reported). Mild application site burning was the most common reaction reported in 35% to 100% of patients (RR 4.2; 95% CI, 3.3–5.5).¹

A 2012 double-blind RCT compared civamide 0.075% cream (the cis-isomer of capsaicin) with civamide 0.01% (a less active control cream to promote blinding) in reducing osteoarthritis knee pain in 695 patients (aged ≥50).² Pain was assessed with the Western Ontario McMaster University Osteoarthritis Index (WOMAC) at baseline and after 12 weeks of treatment. WOMAC scores for pain range from 0 to 20, with higher numbers representing more pain; a WOMAC score of more than 13 is considered severe pain. Response was defined as at least 50% improvement in either the WOMAC pain or WOMAC function scores, or at least 20% improvement in both.

Among patients whose baseline WOMAC pain scores were more than 10, 68% of civamide 0.075% users responded versus 54% of civamide 0.01% users (P=0.002). With baseline WOMAC scores more than 13, 78% of civamide 0.075% users responded versus 51% of civamide 0.01% users (P<0.001). Application site burning was the most common adverse reaction, with only 5% of patients stopping the medication due to this reaction. Adverse reactions decreased as the study went forward—they were recorded for 18% of patients in the treatment arm on day 1, 10% by day 14, and 6% by day 84.²

A 2010 double-blind, randomized, placebo-controlled trial of 100 Thai women 44 to 82 years old with mild to moderate knee osteoarthritis compared 0.0125% capsaicin cream with placebo gel for treatment of knee osteoarthritis pain over 4 weeks.³ Pain was assessed on a VAS (range 0–10), and the WOMAC scores for pain at baseline and after 4 weeks of treatment.

The mean difference in VAS scores with capsaicin versus placebo was 0.72 after 4 weeks of treatment (95% CI, 0.17–1.3). The reduction in mean total WOMAC scores was 3.4 points greater (95% CI, 2.34–4.5) in the capsaicin group than the control group. Application site burning was the only reported adverse event, occurring in 67% of patients in the capsaicin group versus 17% in placebo group. No patients discontinued the medication due to an adverse reaction. This study was limited in that only women farmers were included.³

Sandra Minchow-Proffitt, MD
Christopher Young, MD
Mercy Hospital St. Louis Family Medicine Program
St. Louis, MO

EVIDENCE-BASED ANSWER

Glycosylated hemoglobin (HbA1C) 5.3%–6.4% has a similar predictive value to fasting plasma glucose (FPG) >99 mg/dL over 5 to 6 years; an abnormal result on both measures is more predictive of developing type 2 diabetes mellitus (DM2) than an abnormal result on either test alone (SOR: C, consistent cohort studies of disease oriented outcomes).

A 2011 longitudinal cohort study of 6,241 Japanese patients (4,670 men, 1,571 women; age range 24–82 years; mean age 49.9 years) with and without prediabetes (HbA1C 5.7%–6.4% and/or impaired FPG 100–124 mg/dL) were assessed annually for the rate of progression to DM2 during a mean 4.7-year follow-up.¹ Patients with preexisting cardiovascular risk factors (ie, smoking history, hypertension, hyperlipidemia, history of coronary heart disease and stroke) were included. Of 2,092 patients with baseline prediabetes, 292 new incident cases of diabetes...