events was very small, and no conclusive statements could be made about risk of serious adverse events with the use of PEG (RR 0.47, CI 0.16–1.33).

Certainty in evidence of effects. The certainty of evidence for CSBMs, SBMs, responder rate, and global relief was moderate (because of imprecision). The certainty of evidence for serious adverse events was low because the CI includes both low and high risk of serious adverse events. The overall certainty of evidence for PEG was moderate.

Discussion

PEG is a long-chain polymer of ethylene oxide, which acts as an osmotic laxative. PEG is approved at a dose of 17 g daily for the treatment of occasional constipation by the FDA in the United States and is widely available OTC. Two of the studies used PEG with electrolytes given twice daily (37,38) while the other larger study evaluated the efficacy of PEG 3350 without electrolytes administered once daily (39). The 2 studies of PEG 3350 electrolytes measured the frequency of SBMs per week, but not CSBMs per week (37,38), while the PEG 3350-only study measured CSBM and SBM frequency along with other outcomes (39). Despite the differences in the PEG preparations, doses, and treatment durations, the studies all demonstrated that PEG was associated with a greater efficacy in increasing CSBMs, SBMs, responder rate, improvements in stool form, straining, and global relief compared with placebo, but not abdominal pain. Although PEG is approved by the FDA for the treatment of occasional constipation and not CIC, it has been shown to be efficacious in individuals with CIC for up to 6 months (39). There are additional treatment trials comparing the efficacy of PEG with tegaserod, prucalopride, and lactulose, in which PEG demonstrated a similar or greater efficacy in individuals with CIC than these other medications (41,42), although these trials used different primary end points.

There were no differences in side effect profiles observed between PEG and placebo, although data are limited. Individuals treated with PEG may experience bloating, flatulence, and diarrhea. These effects are consistent with and expected from laxative therapy, and most of these events were mild or moderate. However, PEG is widely available without the need for a prescription and is relatively inexpensive. It is, therefore, reasonable to use PEG earlier in the algorithm for the management of CIC, either after a trial of fiber supplementation or in combination with fiber supplementation.

Recommendation 3: In adults with CIC, the panel suggests the use of MgO over management without MgO (conditional recommendation, very low certainty of evidence certainty).

Implementation considerations

- The trials were conducted for 4 weeks, although longer term use is probably appropriate.
- The panel suggests starting at a lower dose, which may be increased if necessary.
- Avoid use in patients with renal insufficiency due to risk of hypermagnesemia.

Magnesium oxide

Summary of evidence. Two randomized, placebo-controlled trials evaluated the use of MgO for the management of CIC (43,44). Both trials were completed in Japan. The dose of MgO studied was 1.5 g/d for 4 weeks. The 2 trials randomized a total of 47 participants to MgO and 47 participants to the placebo arm, and 93% of the participants were females. At baseline, participants randomized to the placebo group had 4.6 SBMs per week. Those randomized to MgO had 4 SBMs per week at baseline.

Benefits and harms. Compared with placebo, treatment with MgO may increase the number of CSBMs per week (MD 4.29, 95% CI 2.93–5.65) and SBMs per week (MD 3.59, 95% CI 2.64–4.54). Participants treated with MgO achieved a higher treatment response compared with placebo (RR 3.93, 95% CI 2.04–7.56). In absolute terms, 499 more participants per 1,000 might respond to MgO (from 177 to 1,000 more). There was little to no difference in the degree of diarrhea leading to treatment dose change or discontinuation between the 2 study groups (RR 1.07, 95% CI 0.65–1.74). Participants treated with MgO may have better quality-of-life scores as measured by PAC-QOL (MD 16.23, 95% CI 11.44–21.01) and better stool consistency based on the Bristol Stool Form Scale (MD 1.89, 95% CI 1.44–2.33).

Certainty in evidence of effects. The certainty of evidence was very low for the outcomes of CSBMs per week and SBMs per week because of concerns related to inconsistency, indirectness, and imprecision. The certainty of evidence was moderate for the outcomes of responder rate and adverse events due to diarrhea because of imprecision and inconsistency, respectively. The outcomes of quality of life and stool form were rated as low certainty because of indirectness and imprecision. The overall certainty of evidence for MgO was very low.

Discussion

Magnesium is a naturally occurring element that plays an important role in a wide range of biological and biochemical processes (45). Within the lumen of the GI tract, nonabsorbed magnesium creates an osmotic gradient, which leads to net secretion of water and electrolytes, which can exert a beneficial effect on constipation-related symptoms. MgO dosing in the available RCTs was 1.5 g/d. Although not studied in RCTs, lower MgO doses of 500 mg/d to 1 g/d are often used in clinical practice. Only MgO has been evaluated in RCTs; the bioavailability and clinical efficacy of other formulations of magnesium (e.g., citrate, glycinate, lactate, malate, sulfate) for CIC are unknown. Data on adverse effects of MgO from the available trials are limited. The available data suggest no increased reports of diarrhea with MgO compared with placebo (43). Systemic regulation of magnesium levels is maintained by renal excretion (46). Therefore, hypermagnesemia is more likely to occur in individuals with significant renal impairment and magnesium supplements should be avoided in those with a creatinine clearance of $<$20 mg/dL (47).

The combination of efficacy, tolerability, availability of OTC, and low cost make MgO an attractive first-line option for individuals with CIC. Limitations to consider include the small number of clinical trials and included participants with CIC, all trials being conducted in Japan, formulations other than MgO not being evaluated, the dose of MgO used in trials being higher than