Should we treat elevated cholesterol in elderly patients?

EVIDENCE-BASED ANSWER HMG-CoA reductase inhibitors, or statins, have been shown to decrease all-cause mortality in individuals aged 65 and older with known coronary heart disease (CHD) and elevated cholesterol levels. (Grade of recommendation: A, based on randomized controlled trials.) The clinical benefit of statin use in older persons without known CHD, however, is uncertain. Decisions about testing for lipid levels and treatment should include discussions with the patient about the potential benefits and risks of treatment, taking into account the individual's overall risk of CHD. (Grade of recommendation: C, based on extrapolations from cohort studies.)

EVIDENCE SUMMARY Two randomized controlled trials and 1 cohort study demonstrated a decrease in all-cause mortality in individuals aged 65 and older with known CHD by treating elevated cholesterol levels with either pravastatin or simvastatin.[1–3] The overall decrease in absolute risk of death was similar (range, 4.1%–6.2%; numbers needed to treat [NNT] = 17–25). The LIPID trial demonstrated a reduction in CHD-related death (relative risk [RR] = 0.76; 95% CI, 0.62–0.93; NNT = 37) and myocardial infarctions (RR = 0.74; 95% CI, 0.60–0.91; NNT = 36) in elderly patients taking pravastatin 40 mg once daily for 6 years compared with placebo.[3]

Unfortunately, no comparable evidence is available to guide practitioners in their care of older patients without known CHD. A 1993 report on results of the Framingham study showed the association between all-cause mortality and cholesterol level only in individuals younger than 50 years.[4] Two other cohort studies showed an association between elevated cholesterol levels and increased CHD mortality.[5,6] It is unclear whether all-cause or CHD mortality is the better outcome to measure.

The best available evidence addressing the benefit of lowering lipid levels in persons with elevated cholesterol but without CHD is from the West of Scotland Coronary Prevention study, which included patients aged 45 to 64 years.[7] This study showed a 0.5% reduction in CHD mortality (NNT = 200) and a 0.9% reduction in all-cause mortality (NNT = 111). Neither reduction reached statistical significance.

Several reports have demonstrated that statins safely and effectively lower cholesterol levels in patients aged 65 and older.[1–3,8,9] Moreover, statins do not decrease health-related quality of life.[10] Approximately 1% to 4% of those who take statins experience side effects, including abnormal liver function, arthralgias, myalgias, rash, sinusitis, and diarrhea.

RECOMMENDATIONS FROM OTHERS The National Cholesterol Education Program published its updated guidelines in 2001, lending support for statin treatment of elevated low-density lipoprotein cholesterol levels in selected men aged 65 or older and women aged 75 or older without CHD.[11] The target low-density lipoprotein level varied from 100 to 160 mg/dL depending on presence of other cardiac risk factors. The recommendation emphasized lifestyle changes, noninvasive testing for subclinical atherosclerosis, and consideration of treatment for individuals with extensive subclinical disease or multiple risk factors, rather than focusing merely on chronological age.

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What are the treatment options for SSRI-related sexual dysfunction?

EVIDENCE-BASED ANSWER Substituting bupropion, nefazodone, or mirtazapine is beneficial. (Grade of recommendation: B, randomized controlled trials [RCTs].) Augmentation therapy with amantadine, bupropion, and buspirone is no better than placebo. (Grade of recommendation: B, RCTs.) Augmentation therapy with multiple other agents may be beneficial. (Grade of recommendation: D, open-label nonrandomized studies, case series, and case reports.) SSRI "drug holidays" may also be effective (Table 1). (Grade of recommendation: D, open-label nonrandomized studies.)

EVIDENCE SUMMARY SSRI-related sexual dysfunction may be dose dependent and diminish with time, but these aspects have not been evaluated prospectively.Data suggest that bupropion, nefazodone, and mirtazapine have little to no effect on sexual functioning.[1] Changing from SSRIs to one of these agents may alleviate SSRI-induced sexual dysfunction. In a randomized double-blind study, patients experiencing sexual dysfunction on sertraline improved when switched to nefazodone 400 mg daily.[2] Additional open-label nonrandomized studies of all 3 agents suggest improved sexual functioning in 60% to 85% of patients with little to no loss of antidepressant efficacy.[1,3-6] The potential for placebo effects makes interpreting these open-label trials more difficult.

Three augmentation therapies have been tested in double-blind placebo-controlled trials. In the first, buspirone augmentation resulted in a statistical improvement in sexual functioning at weeks 2 and 3 of therapy, but not at weeks 1 and 4 (mean dose 48.5 mg per day).[7] In the second, adding buspirone 20 to 30 mg per day, amantadine 50 to 100 mg per day, or placebo resulted in equal improvement in women's sexual function.[8] Finally, in a third trial, adding bupropion or placebo showed equal improvement in sexual function.[9] Multiple other agents have been tested in open-label nonrandomized studies, case series, and case reports. Most showed a beneficial effect, but results must be interpreted with caution. One open-label nonrandomized study of weekend "drug holidays" showed no benefit for fluoxetine and inconsistent results for paroxetine and sertraline.[10]

RECOMMENDATIONS FROM OTHERS Tertiary literature sources recommend the strategies described above.[11]

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Clinical Commentary by Michael Fisher, MD, additional references, search strategy, and detailed evidence table at http://www.fpin.org.

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TABLE

Summary of treatment options for SSRI-induced sexual dysfunction

Strategy	Drugs considered	RCT data	Other data
Switch therapy	Bupropion SR, bupropion, mirtazapine, nefazodone	Nefazodone effective	All agents effective in nonrandomized open-label trials
Augmentation	Buspirone, amantadine, bupropion, cyproheptadine, dextroamphetamine, granisetron, ginkgo biloba, methylphenidate, mirtazapine, nefazodone,pemoline, sildenafil, yohimbine	Small, transient effect with high-dose buspirone.	Other RCT with buspirone, amantadine, and bupropion showed no difference vs placebo. Most agents effective in nonrandomized open-label trials, case-series, or case reports. Placebo effect unknown
Drug holiday	Fluoxetine, paroxetine, sertraline	None available	Improvement in 2 of 4 weekends for sertraline and paroxetine only

What is the best therapy for constipation in infants?

EVIDENCE-BASED ANSWER The best treatment for minor, self-limited constipation (infant dyschezia) may be observation and parental education about its benign nature. (Grade of recommendation: D, expert opinion.) For cases requiring treatment, limited evidence suggests that 2 weeks of 2% or 4% lactulose normalizes stool passage and consistency. (Grade of recommendation: C, single cohort study.) No data are available about the benefits or harms of rectal thermometer stimulation, glycerin suppositories, sorbitol or sorbitol-containing juices, barley malt extract, or corn syrup. The significant risks of sodium phosphate enemas and mineral oil consumption make their use contraindicated. (Grade of recommendation: D, case reports and expert opinion.)

EVIDENCE SUMMARY Infants experience normal physiologic variation in stool frequency and consistency, moderated in part by diet.[1] Childhood functional defecation disorders represent a continuum from infant dyschezia, to functional constipation, to functional fecal retention[2,3] (Table 1). Most infants have dyschezia or functional constipation. Infant dyschezia, a self-limited condition related to immature muscle coordination, requires only parental reassurance.

We found no placebo-controlled trials of osmotic laxatives in infants. One uncontrolled trial of 220 functionally constipated, bottle-fed infants younger than 6 months showed normalization of stools in 90% of infants within 2 weeks of treatment with 2% or 4% lactulose.[4] No other evidence has been published about the benefits or harms of sorbitol-containing juices, fiber, osmotic laxatives, formula-switching, rectal stimulation with rectal thermometers, or glycerin suppositories.

We found no trials of mineral oil or sodium phosphate enemas in constipated infants. Mineral oil has been associated with lipoid aspiration pneumonia in infants less than 1 year of age.[5,6] Sodium phosphate enemas in children under 2 years of age have been associated with electrolyte disturbances, dehydration, and cardiac arrest.[7]

RECOMMENDATIONS FROM OTHERS The North American Society for Pediatric Gastroenterology and Nutrition recommends glycerin suppositories for rectal disimpaction for acutely constipated infants; sorbitol-containing juices, such as prune, pear, and apple, for decreasing constipation; barley malt extract, corn syrup, lactulose, or sorbitol (osmotic laxatives) as stool softeners; and avoidance of enemas, mineral oil, and stimulant laxatives due to potential adverse effects[8] (Table 2).

TABLE 1

Rome II childhood functional defecation disorders[2]

Disorder, by age	Characteristics
Infant dyschezia (< 6 months old)	10+ minutes of straining and crying before successful passage of stools.
Functional constipation (infancy to preschool years)	2+ weeks of mostly pebble-like, hard stools for stools; or firm stools ≤ 2 times/wk; and no evidence of structural, endocrine, or metabolic disease.
Functional fecal retention (infancy to age 16)	12+ weeks of passage of large-diameter stools at intervals < 2 times/wk; and retentive posturing, avoiding defecation by purposefully contracting the pelvic floor, then gluteal muscles.

TABLE 2

Recommended interventions for infant constipation[8]

Laxative	Dosage	Side effects	Comment
Glycerin suppositories	Standard	None reported	For rectal disimpaction
Sorbitol-containing juices	Variable	None reported	Prune, apple, pear
Barley malt extract	2–10 mL/240 mL milk or juice	Unpleasant odor	Suitable for bottle-feeding
Corn syrup	Variable (light or dark)	None reported	Not considered source of *C. botulinum* spores
Lactulose (70% solution)	1–3 mL/kg per day, divided doses	Flatulence, abdominal cramps,hypernatremia	Well-tolerated long-term
Sorbitol	1–3 mg/kg per day, divided doses	Same as lactulose	Less expensive than lactulose

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