How effective is gastric bypass for weight loss?

■ EVIDENCE-BASED ANSWER

Gastric bypass results in weight loss of approximately 33% at 2 years and 25% at 8 years (strength of recommendation [SOR]: **B**, based on a cohort study). Gastric bypass is one type of bariatric surgery, which also includes gastroplasty and gastric banding procedures (**Figure 1**). These procedures all can produce enough weight loss to measurably improve health, but they differ in the amount of long-term weight loss, as well as side effects, which can be serious.

Gastric bypass is more effective than gastroplasty for weight loss and is associated with fewer revisions, but it has more side effects (SOR: **A**, based on a systematic review). Limited evidence suggests that gastric bypass produces more weight loss than gastric banding (SOR: **B**, based on a cohort study).

Bariatric surgery, including gastric bypass, improves conditions comorbid with obesity, including diabetes, abnormal lipid profiles, and low quality-of-life scores. It decreases the incidence of hypertension at 2 years after surgery, but whether this effect is sustained is unclear (SOR: **B**, based on a cohort study and multiple case series). Bariatric surgery also improves obstructive sleep apnea, obesity hypoventilation syndrome, menstrual irregularity, and female urinary stress incontinence (SOR: **C**, based on multiple case series). Bariatric surgery has a complication rate of 13% and a mortality rate of 0.2% (SOR: **B**, based on 1 cohort study).

■ EVIDENCE SUMMARY

A systematic review comparing bariatric surgery with conventional medical therapy for obesity included 1 randomized controlled trial and the Swedish Obesity Study, a large cohort study with matched controls. Surgery produced 23 to 28 kg more weight loss at 2 years.[1] The study demonstrated 33% ± 10% weight loss for gastric bypass and 0% for medical therapy (not described) at 2 years,[2] and 25% ± 6% loss vs 0.9% gain at 8 years.[3] Among bariatric surgical techniques, patients undergoing gastric bypass lost more weight than those with gastroplasty (using staples to partition the stomach, either horizontally or vertically (**Figure 1**) (P=.057, not significant) or gastric banding (placing a constricting ring around the stomach) (P<.05) at 8 years.[3]

The same systematic review assessed multiple randomized controlled trials comparing gastric bypass with gastroplasty and found greater weight loss, fewer revisions, and more side effects from gastric bypass (**Figure 2**).[1] Five trials comparing

What are Clinical Inquiries?

Clinical Inquiries answer real questions that family physicians submit to the Family Practice Inquiries Network (FPIN), a national, not-for-profit consortium of family practice departments, residency programs, academic health sciences libraries, primary care practice-based research networks, and other specialists.

Questions chosen for Clinical Inquiries are those that family physicians vote as most important through a web-based voting system.

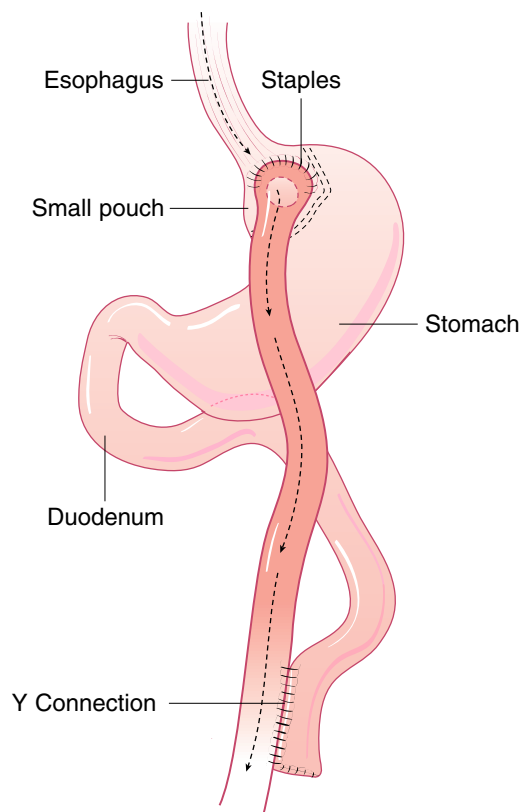**Answers are developed by a specific method:**

Type I answers

- FPIN medical librarians conduct systematic and standardized literature searches in collaboration with an FPIN clinician or clinicians.
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- Finally, a practicing family physician writes an accompanying commentary.
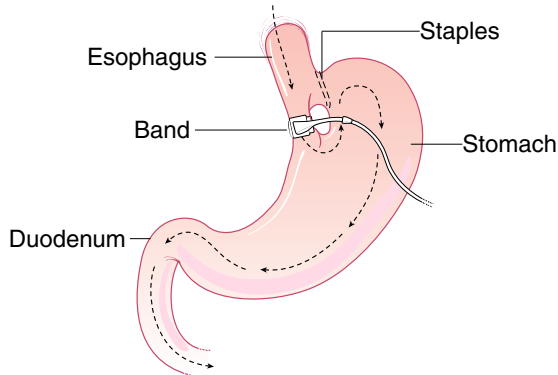
FIGURE 1

Bariatric surgical techniques for weight loss

Gastric bypass (Roux en Y)

Esophagus · Staples · Small pouch · Stomach · Duodenum · Y Connection

Gastroplasty (vertical banded)

Esophagus · Staples · Band · Stomach · Duodenum

Gastric banding (horizontal)

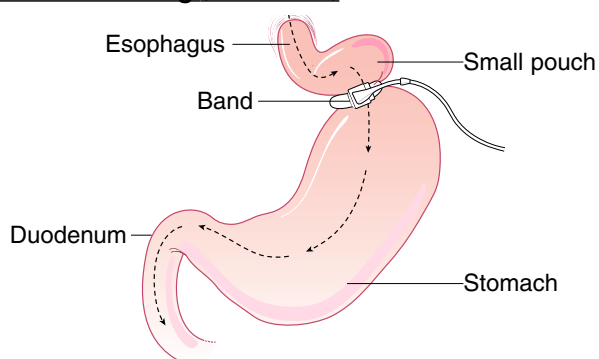Esophagus · Small pouch · Band · Duodenum · Stomach

ILLUSTRATION BY JENNIFER FAIRMAN

gastric bypass with horizontal gastroplasty demonstrated significantly greater weight loss from gastric bypass. Five other trials comparing weight loss from gastric bypass with vertical gastroplasty produced mixed results, with 3 trials favoring gastric bypass and 2 showing no difference.[1] Fewer patients required revision after gastric bypass (0%–4%) compared with vertical gastroplasty (9%) or horizontal gastroplasty (19%–40%). One included trial found that postoperative dumping syndrome (28% vs 0%, $P<0.05$) and heartburn (59% vs 32%, $P<.05$) were more common with gastric bypass than with gastroplasty.[1]

Bariatric surgery, including gastric bypass, improves a variety of obesity-related comorbid conditions. Diabetes prevalence decreased among gastric bypass patients at 2 years (0.0%

vs 4.7%, $P<0.005$) and 8 years (3.6% vs 18.5%, $P<.0005$) compared with those receiving medical therapy.[2,3] In a case series involving 154 diabetic gastric bypass patients, diabetes resolved for 83% by 1 year, and for 86% at 5 to 7 years.[4] In several case series, most patients became euglycemic and discontinued insulin or oral agents.

In the Swedish Obesity Study, hypertriglyceridemia decreased postoperatively but hypercholesterolemia did not.[5] In a case series, bariatric surgery reduced triglycerides (50%) as well as total cholesterol (15%) ($P<.05$ for both) at 6 months and significantly increased high-density lipoprotein cholesterol levels at 1 and 5 years.[6]

Bariatric surgery significantly lowered the incidence of hypertension at 2 years (3.2%) compared with conventional treatment (9.9%), but

after 8 years this difference disappeared.[2,3,5] However, in multiple large case series with morbidly obese patients, hypertension resolved or improved. The largest study showed resolution of hypertension for 69% at 1 to 2 years (91% follow-up), 66% at 5 to 7 years (50% follow-up), and 51% at 10 to 12 years (37% follow-up).[4]

Bariatric surgery improved obstructive sleep apnea and obesity hypoventilation syndrome in 2 case series. In one, Epworth Sleepiness Scale scores, minimum O_2 saturation, and other measures improved significantly ($P<.001$) by 3 to 21 months after surgery.[7]

In another case series, menstrual irregularities decreased from 40.4% to 4.6% following surgery ($P<.001$) among women who lost 50% of their excess weight.[8] The incidence of urinary stress incontinence also decreased significantly (61.2% to 11.6%, $P<.001$ in this study[8]). The Swedish Obesity Study found significant improvements in Health-Related Quality of Life scores at 2 years with surgery vs conventional treatment.[9]

Bariatric surgery, including gastric bypass, has significant postoperative morbidity and mortality. Thirteen percent of patients in the Swedish Obesity Study experienced perioperative complications, including pulmonary symptoms (6.2%), abdominal infection (2.1%), wound complications (1.8%), bleeding (0.9%), thromboembolic events (0.8%), and other miscellaneous complications (4.8%). Postoperative complications required reoperation for 2.2% of surgical patients, and there were 4 postoperative deaths (0.2% of the operative patients; 3 due to leakage, and 1 due to a technical laparoscopic error).[2]

Nutritional and vitamin deficiencies are common following gastric bypass, including deficiencies of vitamin B12, iron, folate, and calcium. Lifelong nutritional supplementation is generally necessary following this procedure.[10]

■ RECOMMENDATIONS FROM OTHERS

A 1991 National Institutes of Health consensus conference suggested consideration of obesity surgery for patients with a body-mass index

FIGURE 2

Long-term weight loss with bariatric surgery
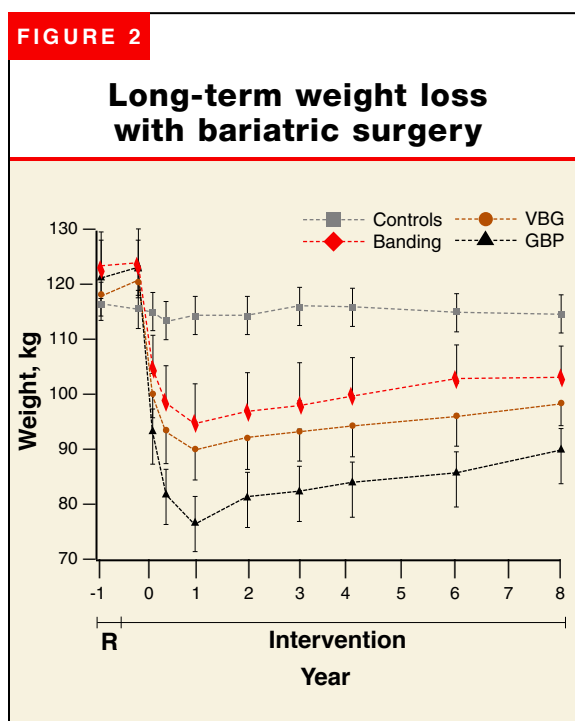
Long-term weight loss with bariatric surgery: comparison of controls, horizontal gastric banding (Banding), vertical banded gastroplasty (VPG), and gastric bypass (GBP). Source: Sjostrom et al 2000.[3]

≥ 40, or ≥ 35 plus severe obesity-related medical comorbidities (such as severe sleep apnea, obesity hypoventilation syndrome, obesity-related cardiomyopathy, or severe diabetes) who have not been successfully treated with non-surgical attempts at weight reduction.

Selected patients should be well-informed and motivated, with acceptable operative risk. A multidisciplinary team with medical, surgical, psychiatric, and nutritional expertise should evaluate patients who are candidates for surgery. An experienced surgeon, working in a clinical setting with adequate support for all aspects of management and assessment, should perform the surgery.

Lifelong medical surveillance is necessary after surgery, and patients should be selected who are likely to comply with this.[11]

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■ CLINICAL COMMENTARY

Bariatric surgery is an important option for select patients

The lack of successful interventions for obesity is frustrating. This is accentuated as obesity is increasingly recognized as the proverbial forest in which we find ourselves hacking at the "trees" of diabetes, hypertension, dyslipidemia, and many other diseases. As we focus on this, the second-leading preventable cause of death, we find ourselves uniquely skilled as family physicians to offer balanced advice and advocacy.[12]

Bariatric surgery is an important option for select patients. For such a patient, I continuously advocate for lifestyle changes, document all non-surgical measures pursued (important for third-party review), discuss realistic expectations and risks, and direct the patient to a trusted bariatric surgery center. For the postsurgical patient, I reinforce the lifestyle commitments, ensure ongoing vitamin and mineral supplementation, and help monitor for possible complications.

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For knee pain, how predictive is physical examination for meniscal injury?

■ EVIDENCE-BASED ANSWER

No single clinical examination element, or combination of such elements, reliably detects meniscal injury. The McMurray test is best for ruling in meniscal pathology. Assuming a 9% prevalence of meniscal tears among all knee injuries (a rate reflecting national primary care data), the posttest probability that a patient with McMurray's sign has a meniscal injury ranges from <30% to 63% (strength of recommendation [SOR]: **B**). In contrast, the absence of any positive physical examination findings effectively rules out meniscal pathology, yielding a posttest probability of 0.8% for lateral meniscus injury, 1.0% for medial meniscus injury, and 3.8% for any meniscal injury among primary care populations (SOR: **B**).

■ EVIDENCE SUMMARY

The accuracy of physical examination findings for meniscal injury varies widely among meta-analyses. In a meta-analysis of 13 studies, no physical examination test—including assessment for joint effusion, McMurray test, joint line tenderness, or the Apley compression test—yielded clinically significant positive or negative likelihood ratios for a meniscal tear (**Table**). The McMurray test performed best, but at 9% to 11% pretest probability of

TABLE	Physical exams for meniscal tear		
	Solomon et al[4]	Scholten et al[1]	Jackson et al[3]
Summary characteristics	9 studies 1018 patients Specialist population Specialist examiners	13 studies 2231 patients Specialist population Specialist examiners	4 studies 424 patients Specialist population Specialist examiners
Positive likelihood ratio (95% CI)			
McMurray	1.3 (0.9–1.7)	1.5–9.5	17.3 (2.7–68)
Joint line tenderness	0.9 (0.8–1.0)	0.8–14.9	1.1 (0.7–1.6)
Aggregate exam	2.7 (1.4–5.1)	—	—
Aggregate exam, medial meniscus tears	—	—	3.1 (0.54–5.7)
Aggregate exam, lateral meniscus tears	—	—	11 (1.8–20.2)
Negative likelihood ratio (95% CI)			
McMurray	0.8 (0.6–1.1)	0.4–0.9	0.5 (0.3–0.8)
Joint line tenderness	1.1 (1.0–1.3)	0.2–2.1	0.8 (0.3–3.5)
Aggregate exam	0.4 (0.2–0.7)	—	—
Aggregate exam, medial meniscus tears	—	—	0.19 (0.11–0.77)
Aggregate exam, lateral meniscus tears	—	—	0.13 (0–0.25)

Note: The results are presented as likelihood ratios, which represent the change in the odds of a diagnosis, based on the outcome of the test. For example, given a positive likelihood ratio of 2, if a test result is positive, the odds of the disease being present is doubled. A positive likelihood ratio >10 provides strong evidence that the disorder is present. A negative likelihood ratio <0.1 provides strong evidence that the disorder is not present. Scores between 0.5 and 2.0 are neutral. In Scholten's meta-analysis, likelihood ratios are given in ranges (no composite value given).

meniscal lesions, based on prevalence estimates among primary care/specialist populations,[2] the posttest probability of a positive exam is still <30%.

A meta-analysis of 4 studies by Jackson compared the utility of the McMurray test and joint line tenderness.[3] For detecting meniscal tears, the McMurray test had a clinically and statistically significant positive likelihood ratio of 17.33, corresponding to a posttest probability of nearly 61%. Negative likelihood ratios for the McMurray test and joint line tenderness (0.5 and 0.8) were not clinically significant, indicating that absence of the

McMurray sign or joint line tenderness alone is of little benefit in ruling out meniscal injury.

In another meta-analysis including 9 studies of meniscal injury diagnosis,[4] individual tests for joint line tenderness, joint effusion, the medial-lateral grind test, and the McMurray test failed to yield statistically significant likelihood ratios for the presence or absence of meniscal tears (**Table** footnotes). Positive and negative likelihood ratios for aggregate physical examination were 2.7 (95% confidence interval [CI], 1.4–5.1) and 0.4 (95% CI, 0.2–0.7), which are statistically, but not

clinically, significant values for ruling meniscal lesions in or out.

Jackson's meta-analysis also calculated the posttest probability of injury for a composite meniscal examination. Based on the positive likelihood ratio of 3.1 (95% CI, 0.54–5.7) and negative likelihood ratio of 0.19 (95% CI, 0.11–0.77), the posttest probability of a medial meniscal tear was 17% in the setting of composite physical exam findings and 1% in the absence of physical exam findings. For a lateral meniscal tear, based on the positive likelihood ratio of 11 (95% CI, 1.8–20.2), and negative likelihood ratio of 0.13 (95% CI, 0.0–0.25), the posttest probability of injury with a positive exam was 41% and with a negative exam 0.8%.

Authors of all meta-analyses noted the lack of standardization in physical examination maneuvers (especially the McMurray test)[5] and, in some cases, no specification of how physical examination tests were performed. Authors analyzed the utility of the aggregate and composite knee examinations without specifying what constituted such an exam. No study included in the meta-analyses used control subjects without meniscal pathology, and few studies were blinded. Lack of blinding may have introduced verification bias; use of specialty patients in all studies made referral bias likely. Studies were heterogeneous and results were associated with wide confidence intervals, introducing an element of random error into the processes of combining and interpreting data.

■ RECOMMENDATIONS FROM OTHERS

The American Academy of Orthopaedic Surgeons' clinical guideline on the evaluation and treatment of knee injuries lists the following findings as associated with a meniscal tear: delayed swelling of the knee, twisting injury, painful popping and catching, effusion, joint line tenderness, positive McMurray's test, and negative radiography.[6] The guideline fails to list the strength and type of supporting evidence for these associations.

The American College of Radiology's Appropriateness Criteria for Acute Trauma to the Knee states that decision rules for meniscal tears and other soft tissue injuries to the knee are being investigated, but it fails to mention specific evaluation strategies for meniscal tears.[7]

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■ CLINICAL COMMENTARY

Meniscus injury likely with suggestive history, joint line tenderness, and an inability to squat because of pain

I often suspect meniscal injuries as a cause of knee pain but am rarely certain based on physical examination alone. I look for a history of joint line pain, locking, or popping with movement. If the patient lacks joint line tenderness, a meniscal injury is unlikely. The McMurray test is usually negative. In the absence of another explanation for the patient's symptoms, a meniscus injury is high on my list in the presence of a suggestive history, joint line tenderness, and an inability to squat because of pain. When my suspicion is high I usually resort to an MRI.

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Do steroid injections help with osteoarthritis of the knee?

■ EVIDENCE-BASED ANSWER

Intra-articular steroid injections appear to provide 2 to 6 weeks of pain relief for patients with knee osteoarthritis (strength of recommendation [SOR]: **A**). Higher-dose steroids with or without joint lavage can provide pain relief up to 24 weeks (SOR: **A**). Steroid injections may be an appropriate adjunct in the treatment of osteoarthritis, which includes nonpharmacologic treatments (education, weight loss, physical therapy) and pharmacologic therapy (nonsteroidal anti-inflammatory drugs [NSAIDs], topical and opioid analgesics).[1,2]

■ EVIDENCE SUMMARY

Osteoarthritis, also known as degenerative joint disease, is the most prevalent form of arthritis in the United States.[3] For the elderly, it is a common cause of pain and disability, affecting patients' ability to perform activities of daily living. Common causes of osteoarthritis include past and present biomechanical stresses affecting the articular cartilage, subchondral bone changes, and biochemical changes in the articular cartilage and synovial membrane.[3]

Treatment of patients with osteoarthritis of the knee should be individualized to the severity of symptoms for each patient. A treatment plan can include patient education, physical and occupational therapy, non-opioid oral and topical agents, NSAIDs, intra-articular corticosteroid injections, viscosupplementation injections, arthroscopic lavage, and total knee replacements.

Our knowledge of the long-term safety and efficacy of intra-articular knee corticosteroid injection is based on limited data. In a randomized, double-blind, placebo-controlled crossover study, investigators randomized 59 patients aged 51 to 89 years to receive either an intra-articular injection of 1 mL of 40 mg methylprednisolone or 1 mL of 0.9% saline. After 3 weeks, patients receiving steroid injection had a minimal change in baseline visual analogue score for pain compared with those receiving saline (median change: –2.0 mm vs 0 mm on a 100-mm scale).[4]

A randomized, single-blinded study involving 84 patients demonstrated significant self-reported "overall improvement" for patients given intra-articular triamcinolone hexacetonide (78%) compared with placebo (49%) after 1 week (*P*<.05).[5] It also confirmed reports that visual analogue score for pain and distance walked in 1 minute improves significantly for both steroid- and placebo-treated groups up to 6 weeks. Only the steroid-treated patients exhibited improved walking distance at 1 week compared with baseline (*P*<.001).

A recent randomized, double-blind, placebo-controlled trial studied the long-term safety and efficacy of treatment of knee osteoarthritis with repeated steroid injections.[6] These investigators studied 66 patients aged 40 to 80 years recruited from rheumatology clinics. One half (n=33) received injections of triamcinolone acetonide 40 mg, and the other half received saline injections every 3 months for 2 years. At 1- and 2-year interval follow-ups, no statistically significant difference was seen between the 2 groups in loss of joint space and no progression of degenerative disease, as demonstrated by measurements of joint space widths by standardized fluoroscopically guided radiographs. Although the primary outcome measure of this study was to assess radiologic joint space narrowing with repeated injections, knee pain and stiffness appeared to improve after 2 years, although these results were not well quantified.

A limitation of most studies testing intra-articular therapy has been sample size. Combining studies may allow the ability to detect levels of pain relief not found in individual

> **Intra-articular steroids are useful for candidates for total knee replacement who are not ready psychologically**

studies. A recent meta-analysis of 6 randomized controlled trials using intra-articular corticosteroid knee injections found short-term relief of pain for 2 weeks (relative risk [RR]=1.66; 95% confidence interval [CI], 1.37–2.01).[7] The number needed to treat (NNT) range for these studies is 1.3 to 3.5. Two additional studies included in this study using higher-dose steroids (prednisone equivalent dose of 37.5 to 80 mg), with or without joint lavage, assessed improvement at 16 to 24 weeks. Although neither individual study showed statistically significant differences, the pooled data from the 2 studies favored symptom improvement at 16 to 24 weeks (RR=2.09; 95% CI, 1.2–3.7; NNT=4.4).[7]

■ RECOMMENDATIONS FROM OTHERS

Guidelines for the treatment of knee osteoarthritis were outlined by a task force for the European League Against Rheumatism (EULAR) Standing Committee for Clinical Trials. The task force recommended intra-articular steroid injection for acute exacerbation of knee pain. This task force performed an evidence-based review and concluded at least 1 randomized control trial recommended intra-articular steroid for patients with osteoarthritis. It was noted that intra-articular steroid injections were effective for only short-term pain relief and that there are no predictors of success of treatment, such as the presence or absence of such factors as joint effusion, degree of radiologic change, age, or obesity.[2]

The American College of Rheumatology Subcommittee on Osteoarthritis Guidelines developed both nonpharmacological and pharmacological recommendations for the treatment of osteoarthritis of the knee.[8] These recommendations include: use of intra-articular steroid injection for patients with acute exacerbations who had evidence for joint inflammation, and joint aspiration accompanying the intra-articular injection for "short-term relief."

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■ CLINICAL COMMENTARY

Intra-articular steroids provide extra relief for patients with acute exacerbations

This well-constructed review demonstrates that intra-articular steroid injections provide up to 3 weeks of pain relief for patients with osteoarthritis of the knee. While this may not seem like much, in practice it can be quite helpful in some situations. It provides supplemental pain relief for patients with acute exacerbations of their disease. It is also useful as a temporizing measure for patients who are candidates for total knee replacement but are not quite ready for it psychologically.

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Does acyclovir help herpes simplex virus cold sores if treatment is delayed?

■ EVIDENCE-BASED ANSWER

When herpes simplex virus (HSV) type 1 lesions are in the papule or vesicle stage, there is no benefit to starting oral acyclovir (strength of recommendation [SOR]: **C**, based on expert opinion). However, topical acyclovir 5% cream applied 5 times a day decreases pain and the duration of hard crust (SOR: **B**, extrapolated from randomized controlled trials [RCTs]).

If started at the onset of symptoms (during the prodrome stage), acyclovir (400 mg 5 times daily for 5 days) decreases pain and healing time to loss of crust and valacyclovir (2 g twice daily for 1 day) reduces the lesion duration and time to healing and may prevent lesion development (SOR: **A**, based on RCTs).

■ EVIDENCE SUMMARY

Cold sores, or herpes labialis, are caused by HSV. Recurrent lesions progress quickly through several stages (prodrome, erythema, papule, vesicle, ulcer, crust, residual swelling, healed).[1] Because of the rapid development of the vesicle stage (<12 hours) and the rapid decrease in detectable virus after 48 hours, studies of antiviral therapy empirically require early treatment within the first several hours of signs or symptoms of a recurrence. For this reason, there are no controlled trials of oral medications given later than 12 hours after the onset of recurrent symptoms.

Although limited, the clearest indication of appropriate timing for HSV 1 treatment with acyclovir comes from a well-designed, double-blinded RCT of 174 adults with a history of culture confirmed HSV labialis who initiated self-treatment with acyclovir 400 mg or placebo 5 times a day for 5 days. Patients were asked to defer treatment until the next episode if they awoke with the lesion or first noticed them in the vesicle or ulcer stage.

Ninety-seven percent of the patients started treatment within 1 hour of signs/symptoms of a recurrence. Of the 174 patients, 90 had lesions in the prodrome or erythema stage at the start of treatment and 84 had lesions in the papule or vesicle stage.

Overall, acyclovir did not effect lesion progression, size, or healing time to loss of hard crust or normal skin. However, the mean duration of pain for all patients significantly decreased (2.5 days vs 3.8 days for placebo, $P=.01$). For the subgroup of patients who started acyclovir treatment in the prodrome or erythema stage, the mean duration of pain significantly decreased (2.5 days vs 3.9 days for placebo, $P=.02$), as did healing time to loss of crust (5.8 days vs 7.9 days for placebo, $P=.03$). Among those who started acyclovir in the papular stage, the trend was toward drug benefit, but this was not statistically significant (mean pain duration: 2.5 vs. 3.6, $P=.36$; mean healing time to loss of crust: 8.0 vs. 7.2, $P=.52$).[2] This evidence supports early (prodrome or erythema stage) but not late (macule, papule, vesicle, or crusted stage) treatment of HSV 1 with oral acyclovir.

Topical application of 5% acyclovir cream significantly decreases clinician-assessed duration of the episode and duration of patient-reported pain, based on 2 double-blind, multicenter RCTs that used a vehicle control. In these trials, 686 and 699 patients self-initiated treatment 5 times a day for 4 days beginning within 1 hour of the onset of a recurrent lesion. In the first study, the mean clinician-assessed duration of the episode with topical acyclovir was 4.3 vs 4.8 days for placebo (hazard ratio [HR]=1.23; 95% confidence interval [CI], 1.06–1.44), and the mean duration of patient-assessed pain was 2.9 vs 3.2 days (HR=1.20; 95% CI, 1.03–1.40). The second study showed a mean clinician-assessed duration with topical acyclovir of 4.6 vs 5.2 days for control (HR=1.24; 95% CI, 1.06–1.44), and the mean duration of patient-assessed pain was 3.1 vs 3.5 days (HR=1.21; 95% CI, 1.04–1.40). Benefits were seen regardless of whether treatment was initiated early (prodrome or erythema stage) or late (macule, papule, vesicle or crusted stage).[3]

> ### UpToDate reports that HSV 1 studies take into account that acyclovir acts only during active viral replication

Recent studies of valacyclovir (the L-valine ester of acyclovir, which has 3 to 5 times greater bioavailability) offer the most promise for effective self-initiated treatment of recurrent herpes labialis. In a report of 2 well-designed, multicenter RCTs, valacyclovir at the FDA-approved dosage of 2 g twice daily for 1 day at the onset of symptoms (before visible signs of a cold sore) significantly decreased the mean duration of the lesion and time to lesion healing. In the first study (n=603), episode duration was decreased by 1.1 days (5.0 days vs 6.1 days for placebo; 95% CI, −1.6 to −0.6) and in the second study (n=605) by 1.0 day (5.3 vs 6.3 days for placebo; 95% CI, −1.0 to −0.5). In the first study, the time to lesion healing was decreased by 1.3 days (4.8 vs 6.1 days for placebo; 95% CI, −1.9 to −0.7) and in the second study by 1.2 days (5.1 vs. 6.4 days; 95% CI, −1.8 to −0.7). There also was a trend towards preventing the development of lesions, but this was not statistically significant.[4]

■ RECOMMENDATIONS FROM OTHERS

The *BMJ* Clinical Evidence Guideline reiterates that no trials compare early vs late treatment, so no firm conclusions about the efficacy of delayed treatment can be drawn.[5] UpToDate reports that HSV 1 studies take into account that acyclovir acts only during active viral replication, which largely precedes symptoms, and thus suggest that it has little effect if begun after the appearance of lesions.[6]

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■ CLINICAL COMMENTARY

For late presenters, review local care and hygiene; for all patients, review management of recurrences

Patients seek treatment for herpes labialis due to bothersome physical symptoms and psychosocial implications. Many patients can identify prodromal symptoms such as localized itching, burning, irritation, or pain. Diagnosis of the initial episode is frequently delayed as patients are evaluated after the time period when studies have shown the most benefit from antivirals. For the late presenters, I review local care and hygiene, and for all patients I review management of recurrences.

Patient-initiated treatment is effective for those who can recognize the earliest signs and symptoms and start treatment immediately with either a topical or systemic antiviral. Both formulations decrease the lesion time to healing and pain if started at the first onset of symptoms.

Cost is an important consideration when selecting a particular formulation. Approximate price for the regimens presented here are $12 for 5 days of oral acyclovir, $27 for 1 day of oral valacyclovir, and $37 for a 2-g tube of acyclovir cream, which can be used for more than 1 episode.[7] Other factors to consider are pill burden, duration of treatment, patient preference, and lifestyle. Patients can keep a refill or medicine on-hand to manage recurrences with the advice to begin immediately with onset of signs or symptoms.

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How should thyroid replacement be initiated?

■ EVIDENCE-BASED ANSWER

Levothyroxine (LT4) should be used alone as initial replacement for patients with hypothyroidism (strength of recommendation [SOR]: **A**). The optimal initial dose is 1.6 µg/kg/d for healthy people aged 60 years or younger (SOR: **B**). Patients aged more than 60 years may require less levothyroxine to achieve therapeutic serum thyroid hormone replacement, so initial replacement should be decreased to 25 to 50 µg daily (SOR: **C**).

Since patients with known heart disease may develop dysrhythmias, angina, and myocardial infarctions when started on full replacement doses, experts recommend starting 12.5 to 25 µg daily for this population (SOR: **C**). Brand-name (Synthroid, Levoxyl, etc) and generic LT4 are bioequivalent (SOR: **B**), although the US Food and Drug Administration (FDA) does not consider these products to be interchangeable until proven therapeutically equivalent.

■ EVIDENCE SUMMARY

Initial thyroid replacement with synthetic LT4 is recommended because LT4 is safe, effective, reliably relieves symptoms, and normalizes lab tests for hypothyroid patients.[1,2]

Two recent randomized trials comparing LT4 alone or LT4 and LT3 together for a total of 86 adult hypothyroid patients found similar outcomes. One study, which enrolled patients with hypothyroidism and mild depressive symptoms, assessed scores on the Symptom Check-List-90, the Comprehensive Epidemiological Screens for Depression, and the Medical Outcomes Study health status questionnaire at baseline and multiple times over the duration of the study. For these outcomes, no differences were found between the LT4 alone and combination LT4-LT3 treatment groups within 90% confidence intervals.[3] A second study assessed changes in body weight, lipid pro-file, hypothyroid-specific health-related quality-of-life scores, and 13 neuropsychological measures pre- and posttreatment. This study detected no difference in body weight and serum lipids at baseline and after treatment. The hypothyroid-specific health-related quality-of-life scores similarly improved for both treatment groups. Twelve of 13 neuropsychological tests demonstrated no differences between treatment groups; the Grooved Peg Board Test of manual dexterity and fine visual-motor coordination demonstrated a slight improvement for the LT4 alone treatment group.[4]

The initial dose of LT4 can be based on the age and health status of the patient. The mean replacement dose of LT4 is 1.6 µg/kg/d for healthy patients aged ≤60 years.[5–7] Patients aged >60 years should be started on 25 to 50 µg daily. An uncontrolled cohort study of 84 patients found that for patients aged >60 years, 25- to 50-µg doses of LT4 resulted in similar serum thyrotropin (TSH) levels as the higher (1.6 µg/kg/d) doses required for younger patients.[7] Based on expert opinion, patients of any age with heart disease should be given lower doses of 12.5 to 25 µg daily as initial treatment.[1,2]

The choice of the LT4 preparation continues to be debated. In 1997, a bioequivalence study compared 2 generic brands to 2 name brands by having 22 women with hypothyroidism, who were euthyroid on replacement medication, take each preparation for 6 weeks.[8] The area under the curve, peak serum concentration, and time to peak concentration for 3 indexes of thyroid function (thyroxine, triiodothyronine, and free T4 index) were not significantly different and met the FDA criterion for relative bioequivalence. However, they did not examine therapeutic equivalence and from a clinical perspective, some researchers and pharmaceutical companies felt that the authors could not comment on whether the products were interchangeable.[8,9] The FDA now requires thyroxine bioavailability and bioequivalence studies to evaluate product substitution.[10] The FDA lists Levothyroxine Sodium (Mylan) to be therapeutically equivalent and therefore interchangeable with Unithroid.[11]

■ RECOMMENDATIONS FROM OTHERS

The American Association of Clinical Endocrinologists Thyroid Task Force recommends the use of a high-quality brand preparation of LT4 rather than desiccated thyroid hormone, combinations of thyroid hormones, or LT3.[12] It recommends a mean replacement dosage of LT4 of 1.6 µg/kg of body weight per day with initial dose ranging from 12.5 µg daily to a full replacement dosage based on the age, weight, and cardiac status of the patient.

UpToDate states that although LT4 products are standardized, subtle differences between preparations exist, and products should be interchanged only with sufficient monitoring after the change. In addition, they recommend generally avoiding generics because the pharmacy may interchange products without physicians being aware.[1] The Physicians' Information and Education Resource from the American College of Physicians states "Name-brand LT4 products provide more consistent potency than generic preparations. The cost of brand-name LT4 products is only slightly more than that of generic preparations."[2]

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■ CLINICAL COMMENTARY

Instruct patients about the timing of levothyroxine and potential interactions

The starting dose of levothyroxine for hypothyroid patients is based on age, severity of the disease, duration of the disease, and existing comorbid conditions. For healthy adults 60 years of age or younger, the optimal starting dose is 1.6 µg/kg/d. For patients more than 60 years of age, the initial dose is 25 to 50 µg/d. To avoid cardiac complications among persons with known heart disease, the recommended initial levothyroxine dose is 12.5 µg/d. In my experience, these guidelines work well in initiating treatment for hypothyroidism.

Few of my patients have noted any difference between generic and brand-name thyroid supplements. Knowing what other medications the patient is taking is important, since medications such as estrogen can decrease the bioavailability of levothyroxine by increasing binding proteins. It is also important to instruct patients about the timing of levothyroxine intake, because some medications can affect absorption (eg, cholestyramine, calcium, or iron).

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Is nedocromil effective in preventing asthmatic attacks in patients with asthma?

■ EVIDENCE-BASED ANSWER

Nedocromil (Tilade) is effective for the treatment of mild persistent asthma. It has not been shown to be effective in more severe forms of asthma for both children and adults. Although no studies looked specifically at exacerbation rates, multiple clinical and biologic outcomes (symptom scores, quality of life measures, bronchodilator use, forced expiratory flow in 1 second [FEV1], and peak expiratory flow rate [PEFR]) improved with nedocromil use compared with placebo.

The most effective dose for preventing exacerbations appears to be 4 mg (2 puffs) 4 times a day (SOR: **A**, multiple randomized controlled trials [RCTs] and meta-analyses). More severe forms of asthma respond better to inhaled steroids than to nedocromil (SOR: **A**, multiple RCTs). Nedocromil may allow some patients with severe asthma to use lower doses of inhaled steroids (SOR: **C**, conflicting RCTs). Nedocromil is also effective for the treatment of exercise-induced asthma (SOR: **A**, multiple RCTs and meta-analyses).

In general, about 50% to 70% of patients respond to nedocromil (SOR: **A**, multiple RCTs and meta-analyses). Unfortunately, which patients respond is not predictable from clinical parameters.[1] Nedocromil is worth trying in mild persistent asthma, particularly for children where the parents are worried about the growth issues associated with inhaled steroids. Side effects (sore throat, nausea, and headache) are mild and infrequent. Maximal efficacy is usually seen after 6 to 8 weeks.

■ EVIDENCE SUMMARY

A systematic review encompassing 127 trial centers and 4723 patients concluded that inhaled nedocromil was effective for a variety of patients with asthma. Significant improvements were noted in FEV_1, PEFR, use of bronchodilators, symptom scores, and quality of life scores. The reviewers found nedocromil to be most effective for patients with moderate disease already taking bronchodilators,[2] corresponding to the "mild persistent asthma" category (**Table**).

A contemporaneous European RCT, not included in the review, compared 4 mg of inhaled nedocromil 4 times daily with inhaled placebo among 209 asthmatic children for 12 weeks.3 After 8 weeks, they found a statistically significant reduction in total daily asthma symptom scores (50% nedocromil vs 9% placebo; $P<.01$). The proportion of parents and children rating treatment as moderately or very effective was 78% in the treatment group and 59% in the placebo group (number needed to treat [NNT]=5.2; $P<.01$); clinicians' ratings were 73% for nedocromil and 50% for placebo (NNT=4.3; $P<.01$). The frequency of side effects—including nausea, headache, and sleepiness—did not reach statistical significance; however, the nedocromil group reported up to a 20% incidence of sore throat. Most of the studies reported no dropouts due to side effects.

When patients are already using inhaled steroids, the evidence is less clear whether nedocromil confers additional benefits, such as fewer exacerbations or lower inhaled steroid doses. Two small studies of patients either already on inhaled steroids[4] or considered to be steroid-resistant[5] found nonsignificant trends towards reductions in bronchodilator use, increased PEFR, increased FEV_1, and improved quality of life. Although both studies were underpowered, the study on steroid-resistant asthma did find a statistically significant 20% improvement in PEFR and decreased bronchodilator use for 50% of patients at 8 and 12 weeks.

The inherent waxing and waning nature of asthma makes demonstrating benefits difficult. Furthermore, nedocromil tends to have an all-or-nothing effect rather than a dose-response gradient. Unfortunately, none of these trials found useful predictors to help clinicians determine which patients respond.[1,5]

In a Cochrane Review, 20 RCTs involving 280

TABLE

Classification of asthma

Classification	Symptom frequency	Spirometry findings
Severe persistent	Continual symptoms	PEFR <60% Variability >30%
Moderate persistent	Daily symptoms, more than 1 night per week	PEFR >60% but <80% Variability >30%
Mild persistent	More than twice per week but less than daily; more than 2 nights per month	PEFR >80% Variability 20%–30%
Mild intermittent	Less than once per week; less than or equal to 2 nights per month	PEFR >80% Variability <20%

Source: Global Initiative for Asthma, National Heart, Lung and Blood Institute 2003.[7]

participants showed that 4 mg (2 puffs) of nedocromil inhaled 15 to 60 minutes prior to exercise significantly reduced the severity and duration of exercise-induced asthma for both adults and children. The maximum percentage fall in FEV_1 improved significantly compared with placebo, with a weighted mean difference of 15.5% (95% confidence interval, 13.2–18.1). In addition, the time to complete recovery was shortened from 30 minutes with placebo to 10 minutes with nedocromil.[6]

■ RECOMMENDATIONS FROM OTHERS

The Global Initiative for Asthma and the National Heart, Lung and Blood Institute Expert Panel Report list nedocromil as an option for the treatment of exercise-induced asthma and mild persistent asthma for adults and children. However, it is listed as a second choice to the use of inhaled steroids in the case of mild persistent asthma. It is not recommended for moderate or severe persistent asthma, or for mild intermittent asthma.[7]

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■ CLINICAL COMMENTARY

Nedocromil and cromolyn sodium are safe but many patients do not respond
Inhaled nedocromil and cromolyn sodium have long been recognized as agents with an excellent safety profile. Unfortunately, as pointed about above, many patients do not respond to these agents. In addition, 4-times-daily dosing makes compliance difficult. Clinicians and parents must weigh the theoretical risk of inhaled corticosteroid-induced growth retardation with this potential differential in effectiveness.

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