How should we treat chronic daily headache when conservative measures fail?

EVIDENCE-BASED ANSWER

For the purposes of this review, we considered conservative measures to include such therapies as nonsteroidal anti-inflammatory drugs (NSAIDs), physical therapy, and acetaminophen with codeine. Amitriptyline is the best-supported option for the treatment of chronic daily headaches for those patients who have not been treated by conservative measures (strength of recommendation [SOR]: **A**, based on a meta-analysis of randomized controlled trials [RCTs]).[1]

For patients who overuse symptomatic headache medications, medication withdrawal is effective (SOR: **B,** based on a systematic review of cohort and case-control studies).[2] Additional therapies include other tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and prophylactic treatments for migraine (SOR: **B**).[3]

EVIDENCE SUMMARY

Chronic daily headache is a heterogeneous primary headache disorder, often defined as a headache duration of more than 4 hours and a headache frequency of more than 15 per month; it affects less than 5% of the US population. Four headache subtypes included in the chronic daily headache definition are chronic (transformed) migraine, chronic tension-type headache, new daily persistent headache, and hemicrania continua. Each subtype may be associated with medication overuse.[4]

Chronic daily headache is challenging to categorize and difficult to manage, and scientific evidence to guide treatment is scant. Despite this, a few studies do offer some hopeful alternatives to those patients who have had conservative measures fail (**Table**).

A meta-analysis from 2001 reviewed 38 RCTs of antidepressants as prophylaxis for chronic headache. Nineteen studies investigated TCAs, 18 examined serotonin blockers, and 7 focused on SSRIs. Patients taking antidepressants were twice as likely to report headache improvement (rate ratio [RR]=2.0; 95% confidence interval [CI], 1.6–2.4), with the average amount of improvement considered to be large (standard mean difference=0.94; 95% CI, 0.65–1.2). Serotonin blockers, most of which are not available or commonly used in the US, and TCAs were all effective in decreasing the headache burden, while the results for SSRIs were less clear. Dosages of amitriptyline ranged from 10 to 150 mg daily; most of the studies used 60 to 100 mg daily.[1]

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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.
- FPIN clinician authors select the research articles to include, critically appraise the research evidence, review the authoritative sources, and write the answers.
- Each Clinical Inquiry is reviewed by 4 or more peers and editors before publication in *JFP*.
- FPIN medical librarians coauthor Type I Clinical Inquiries that have required a systematic search.
- Finally, a practicing family physician writes an accompanying commentary.

TABLE

Treatment options for chronic daily headache

Treatment option	Study design, no. of studies	Total no. enrolled	Outcome
Amitriptyline	Double-blind, 7	257	↓ in headache severity, frequency and/or duration
Fluoxetine	Double-blind, 2	92	↑ in headache- free days, mood improvement; ↓ in headache severity
Gabapentin	Double-blind, 1	26	↓ in headache frequency
Botulinum toxin A	Double-blind, 1	16	↓ in headache intensity, frequency and duration
Tizanidine	Double-blind, 1	45	↓ in headache intensity, frequency and daily analgesic use
Sumatriptan	Double-blind,1	42	No statistically significant change in headache intensity
Valproate	Open, 5	191	Mixed results

Adapted from Redillas and Solomon 2000.[3]

Medication withdrawal therapy is a treatment strategy for chronic daily headaches associated with the paradoxical induction of headaches by the frequent, long-term use of immediate relief medications such as aspirin, NSAIDs, acetaminophen, caffeine, codeine, ergotamine, and sumatriptan. A retrospective study tracked 101 men and women who underwent a controlled outpatient withdrawal of their overused medications. Headache diaries kept for 1 to 3 months reflected that 56% of the patients had at least a 50% reduction in headache days after removal of overused drugs. Twenty-two patients who had no success with withdrawal and continued to have headaches were treated with amitriptyline. Subsequently, 10 of these patients experienced a 50% reduction in headache frequency.[5]

A systematic review of the therapeutic approaches to medication-induced headache looked at 18 studies from 1966 to 1998. Although most were uncontrolled small trials, medically monitored withdrawal of all symptomatic headache medications is recommended by the authors. No long-term outcome comparisons between withdrawal strategies are available.[2]

Other therapies for treating chronic daily headache include the skeletal muscle relaxant tizanidine (Zanaflex), which was studied in an industry-sponsored, double-blind, placebo-controlled trial of 92 patients. The medication was used as prophylaxis, titrating up to a dose of 8 mg 3 times daily. The overall headache index (a measure of headache intensity, frequency, and duration) significantly decreased. The headache index decreased in the tizanidine group from 2.6 to 1.2, and in the placebo group from 2.6 to 2.1 (P=.0025). Decreases in headache frequency and headache intensity were less dramatic but still significant. This trial lasted only 12 weeks, so longer-term outcomes are not available.[6]

Stress management, acupuncture, botulinum toxin, behavioral therapy including relaxation ther-

apy, biofeedback, and even Internet-based self-help have all been studied, but most of these therapies do not have significant evidence-based support.

RECOMMENDATIONS FROM OTHERS

Our literature search and review of major textbooks found no formally organized guidelines or recommendations on the treatment of chronic daily headache.

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CLINICAL COMMENTARY

A detailed history and assessment of possible comorbid conditions is crucial

Obtaining a detailed history and the assessment of possible comorbid conditions such as psychiatric disorders, insomnia, and existing stressors is crucial to making the diagnosis of chronic daily headache and choosing therapy. A headache diary provides clinicians with helpful information such as the duration and frequency of the headaches, possible triggering factors, and the class, and numbers of analgesics used. Patients who have more than 2 episodes of migraine per week are appropriate candidates for preventive treatment.

The possibility of analgesic overuse must be considered for patients who use headache medications more than twice a week. Preventive headache medications do not work if analgesics are being overused. Once a diagnosis is made, detoxification needs to be discussed with the patient.

As a patient with chronic migraine, I have found stretching exercise, stress management, and dietary modifications very helpful. The most common foods to avoid are caffeine, chocolate, alcohol, aged or cured meat, bananas, and foods containing monosodium glutamate or tyramine.[3]

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Should we screen for bacterial vaginosis in those at risk for preterm labor?

EVIDENCE-BASED ANSWER

Bacterial vaginosis (BV) is associated with preterm delivery (strength of recommendation [SOR]: **A**, meta-analysis). However, treating asymptomatic, low-risk women with BV does not always prevent preterm delivery (SOR: **A**, randomized controlled trials [RCTs]). There is some benefit to early screening by Gram stain using Nugent's criteria[1] (**Table**) and treating BV-positive women with a history of preterm delivery, premature rupture of membranes, low birth weight infants, or spontaneous abortion. In this group, treatment has been associated with decreased rates of preterm labor, preterm prelabor rupture of membranes, and low birth weight infants (SOR: **B**, conflicting RCTs).

Empirically treating high-risk women without documented infection has been associated with an increase in preterm deliveries and neonatal infections (SOR: **B**, single RCT).

EVIDENCE SUMMARY

Bacterial vaginosis in early pregnancy is a risk factor for preterm delivery.[2] The role of BV in

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TABLE

Nugent's Criteria

Score	*Lactobacillus* morphotypes	*Gardnerella* and *Bacteroides* spp. morphotypes	Curved gram-variable rods
0	4+	0	0
1	3+	1+	1+ or 2+
2	2+	2+	3+ or 4+
3	1+	3+	
4	0	4+	

1+, <1 morphotype present; 2+, 1 to 4 morphotypes present; 3+, 5 to 30 morphotypes present; 4+, >30 morphotypes present. The diagnosis of bacterial vaginosis is present with a score of 7 or greater. From Nugent 1991.[1]

preterm labor is not well understood, but it has been consistently associated with preterm labor and delivery. The detection of BV in early pregnancy seems to be a stronger risk factor for preterm delivery than BV in later pregnancy.

Studies evaluating the screening and treatment of BV in women at risk for preterm delivery have demonstrated varying results. Most treatment studies have excluded women who are in the first trimester. A meta-analysis of 7 RCTs reviewed the evidence of screening for BV in pregnancy.[3] In this meta-analysis, 5 of the trials specified that women were asymptomatic, and the other 2 did not comment on whether the women were symptomatic or not. In general, there was no benefit to routine screening and treatment of BV.

However, a subgroup of high-risk women seems to benefit from screening and treatment. They defined high-risk women as those have had a preterm delivery, premature rupture of membranes, birth weight <2500 g, or spontaneous abortion. Treating BV in women with a high-risk pregnancy decreased preterm delivery (absolute risk reduction [ARR]=0.22; 90% confidence interval [CI], 0.13–0.31; number needed to treat [NNT]=4.5) regardless of antibiotic choice. However, 2 trials of high-risk women who were empirically treated for BV, but did not have BV, showed an increase in preterm delivery less than 34 weeks (number needed to harm [NNH]=11).

A new study evaluating screening for vaginal infections in pregnancy has demonstrated a reduction in preterm delivery.[4] In this study, looking at a general obstetrical population in Austria, 4429 asymptomatic pregnant women between 15 and 19.6 weeks gestation had a vaginal screen for bacterial vaginosis, candidiasis and trichomoniasis. The 2048 women in the intervention group were given the results of the screen from their maternity care provider. The 2097 women in the control group and their providers did not receive the results of the vaginal screen. There were 447 women in the intervention group and 441 women in the control group with positive screens. Using the Nugent criteria, women who were diagnosed with BV received a 6-day course of intravaginal clindamycin 2% cream. Those with positive test results for *Candida* were treated with intravaginal clotrimazole 0.1 g; those with positive results for trichomonas received intravaginal metronidazole 500 mg for 7 days. After treatment, women with a positive test result in the intervention group had a second vaginal smear between 24 and 28 weeks. Persistent BV was treated with oral clindamycin 300 mg twice daily for 7 days. If *Candida* or trichomonas were noted, women were treated with the intravagi-

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nal clotrimazole or metronidazole. A statistically significant reduction was seen in preterm births in the intervention group(3.0% vs 5.3%, 95% CI, 1.2–3.6; *P*=.0001; number needed to screen=44).

A large study in 2000 that looked at the use of metronidazole in the treatment of asymptomatic women for BV did not demonstrate any reduction in preterm birth.[5] In this study, 21,965 asymptomatic women between 8 and 22 weeks gestation were screened for BV with Gram stain using Nugent's criteria. Then, 1953 women with BV were randomized to receive either 1 g of metronidazole orally for 2 days or placebo. Between 24 and 29 weeks, all of the women were then rescreened for BV by Gram stain. Even if the results were negative, women received another course of the metronidazole or placebo. In this study, preterm delivery rates did not improve for either low- or high-risk women. Specifically, a subgroup analysis of 213 women with previous preterm delivery did not show any benefit to treatment with metronidazole.

In 2003, a Cochrane meta-analysis of 5 studies involving 622 women with previous preterm birth showed a decrease in the risk of low birth weight infants born to women receiving antibiotics vs placebo for the treatment of BV (odds ratio [OR]=0.31; 95% CI, 0.13–0.75).[6] Treatment also decreased the risk of preterm-prelabor rupture of membranes (OR=0.14; 95% CI, 0.05–0.38) compared with placebo. Unfortunately, these studies did not always specify whether women were asymptomatic for BV infection. In many of the trials, symptomatic women were excluded as they were automatically treated with antibiotics.

In 2003, 2 RCTs evaluating the early treatment of asymptomatic BV in low- and high-risk patients showed a decrease in preterm labor. The first RCT included 494 asymptomatic pregnant women who presented for prenatal care between 12 and 22 weeks gestation. If women had BV detected by Gram stain using Nugent's criteria, they were randomized to receive either 300 mg oral clindamycin twice daily for 5 days or placebo. In the general population, treatment with clindamycin reduced the rate of late miscarriage and spontaneous preterm delivery by 10.4% (95% CI, 5.0–15.8). In women with a previous preterm delivery or a late miscarriage the proportion of preterm delivery or late miscarriage was reduced (16.6% vs 42%).[7]

The second RCT included 409 asymptomatic women between 13 and 20 weeks gestation with BV by Gram stain using Nugent's criteria. Investigators randomized women to intravaginal clindamycin each night for 3 days. At a second visit, 20 to 24 days after treatment, women were retested for BV and if they were positive, they received a 7-day course of intravaginal clindamycin or placebo based on the previous randomization. In this study, the incidence of preterm birth was reduced from 10% to 4% (relative risk [RR]=0.38; 95% CI, 0.16–0.90; NNT=17). This study only included 21 women with previous preterm delivery and a subgroup analysis was not performed.[8]

Intravaginal clindamycin has been associated with worse pregnancy outcomes for patients who do not have bacterial vaginosis. A randomized trial of the prophylactic intravaginal clindamycin 2% cream to prevent preterm birth in high-risk women showed an increase in spontaneous preterm delivery in women who actually used all of the medication and did not have BV (NNH=12.3; *P*<.05).[9]

■ RECOMMENDATIONS FROM OTHERS

The US Preventive Services Task Force concludes that the evidence is insufficient to recommend for or against routinely screening for BV for high-risk pregnant women. Furthermore, they recommend against screening for average risk women.[10]

The Centers for Disease Control and Prevention recommends that high-risk pregnant women (eg, those women who have had a previous preterm delivery) with asymptomatic BV may be evaluated for treatment. The recom-

mended treatment regimens are metronidazole 500 mg orally twice a day for 5 days, metronidazole gel intravaginally for 5 days, or clindamycin cream intravaginally for 7 days.[11]

The Cochrane Pregnancy and Childbirth Group finds no evidence supporting routine screening and treatment for asymptomatic bacterial vaginosis in pregnancy, except possibly for women with a history of preterm birth.[6]

The American College of Obstetrics and Gynecology summarizes no data supports screening for BV to prevent preterm birth. Their bulletin references a subgroup of women with previous preterm birth who did show benefit from treatment for BV, but the authors speculated that reanalysis with the inclusion of the largest trial to date, which did not show a benefit for this subgroup, might nullify these results.[12]

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Randomized controlled trials show no change in outcomes by treating asymptomatic BV in pregnancy

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CLINICAL COMMENTARY

Until there's more research, only screen women who are high-risk or symptomatic

Although the association of BV and chorioamnionitis and preterm labor is strong, the RCTs do not show any change in outcomes by screening and treating asymptomatic BV in pregnancy except in women who already have a history of preterm labor or premature rupture of membranes. Our practice was screening and treating all pregnant women at the first prenatal visit until about 3 years ago when the RCTs failed to show an impact. The studies that brought BV to the forefront of this discussion show that the inflammatory response caused by BV start in the first trimester or before and treatment is most effective when done early. Perhaps these RCTs are not treating enough women early in pregnancy to see a difference in outcome.

The study we need to have (and which may never be done) would test the treatment of women with BV, either just before conception or early in the first trimester. I am awaiting the next round of information, but for now, I only screen women who are high risk or women who are symptomatic.

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How reliable are self-measured blood pressures taken at home?

EVIDENCE-BASED ANSWER

Self-measured blood pressures (SMBP) can be precise and accurate and, thus, reliably be used as an adjunct to office blood pressure measurements in selected clinical situations (strength of recommendation [SOR]: **B**, extrapolation and limited trials). Clinicians using SMBP need to be aware of the difference in normal reference ranges, with pressures greater than 135/85 mm Hg considered hypertensive.

Whether hypertensive treatment should be based primarily on SMBP is unclear, and currently undergoing study. Clinicians should recommend multiple daily measurements with a validated and standardized device, preferably equipped with memory or transmission capabilities, in order to avoid patient error in transcribing and reporting values. Wrist or finger devices cannot reliably be used (SOR: **B**, limited comparison studies).

EVIDENCE SUMMARY

Office blood pressure (OBP) has traditionally been used in long-term trials to describe the relationship between blood pressure and cardiovascular morbidity and mortality, as well as to establish the efficacy of antihypertensive drug therapy. A prospective randomized trial demonstrating the relationship between therapy based on SMBP to these same outcomes is in progress.[1]

Two large prospective cohort studies of the relationship between SMBP and morbidity and mortality made comparative baseline blood pressure measurements and followed the cohorts without suggestions or attempts to change management. The first was a rural population-based study with 1789 subjects (90% of the population) from Ohasama, Japan.[2] Mean follow-up was 6.6 years with less than 1% dropout rate. The second large cohort study (SHEAF trial) included patients ≥60 years old with the diagnosis of hypertension.[3] A total of 4939 cases were analyzed. Mean follow-up was 3.2 years with less than 1% dropout rate. Both studies show that each mm Hg increase in SMBP was a better predictor of cardiovascular events than an equivalent increase in OBP (**Table 1**).

Office blood pressure measurements exhibit large variability (decreased precision) and are subject to multiple biases (decreased accuracy). Self-measured blood pressures at home became common when "white-coat hypertension" was recognized to be clinically significant. It allows for a larger number of measurements for individual patients, resulting in greater precision than OBP.[4] SMBP correlates better than OBP with surrogate measures of hypertensive control, such as ambulatory blood pressure measurement[5] and left ventricular mass.[6] Thus, SMBP might some day become the gold standard for defining hypertension in the clinical setting. Meanwhile, the correlation between OBP and SMBP can be derived via three different mathematical models using data from multiple studies. The accepted cutoff for SMBP defined hypertension is 135/85 mm Hg.[7]

The THOP trial[8] was a single-blinded, randomized controlled trial of hypertensive treatment based on SMBP vs OBP. Four hundred patients were randomized to SMBP or OBP, with medication adjustments made by a blinded clinician. The trial design called for both treatment groups to be titrated to a diastolic blood pressure of 80 to 89 mm Hg. The follow-up was approximately 1 year. Graphical data indicate that both groups were equally effective in meeting the blood pressure goals outlined in the methods.

Other differences in outcomes were proportional to the known difference in normotensive reference ranges (eg, that OBP tend to run higher than SMBP). Patients in the SMBP group were put on less-intensive drug treatment and

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TABLE 1

Increase in cardiovascular mortality for each 1 mm Hg increase in blood pressure

	Cox Proportional Relative Hazards Ratio [95 % CI]			
	Home systolic BP	Home diastolic BP	Office systolic BP	Office diastolic BP
Ohasama study[2]*	1.021 [1.001–1.041]‡	1.015 [0.986–1.045]	1.005 [0.990–1.020]	1.008 [0.984–1.033]
SHEAF study[3]†	1.02 [1.01–1.02]‡	1.02 [1.01–1.03]‡	1.01 [1.00–1.01]	1.00 [0.99–1.02]

*Results were adjusted for age, sex, smoking status, history of cardiovascular disease, and use of antihypertensive medication.
†Increase in cardiovascular events for each 1 mm Hg increase in blood pressure. Results were adjusted for age, sex, heart rate, smoking status, history of cardiovascular events, presence of diabetes, presence of obesity, and presence of treatment for hypercholesterolemia.
‡Statistically significant.

incurred slightly lower medical costs. SMBP patients were twice as likely to have their blood pressure medication discontinued, possibly indicating SMBP helped to identify white-coat hypertension.

RECOMMENDATIONS FROM OTHERS

In addition to diagnosing white-coat hypertension, World Health Organization/International Society of Hypertension Guidelines Committee has recommended that home blood pressure measurement is useful in the following circumstances:[9]

- unusual variability of blood pressure over the same or different visits
- office hypertension in subjects with low cardiovascular risk
- symptoms suggesting hypotensive episodes
- hypertension resistant to drug treatment.

Standardization and validation protocols are available from the Association for the Advancement of Medical Instrumentation,[10] European Hypertension Society,[11] or the British Hypertension Society (available at www.hyp.ac.uk/bhs/bp_ monitors/automatic.htm). Relatively few of the hundreds of available blood pressure measurement devices available meet these criteria. The most current Association for the Advancement of Medical Instrumentation standards are labeled as ANSI/AAMI-SP10:2002/A1:2003 standards. **Table 2** lists some devices that meet the various protocols. Devices in this market change rapidly, so buyers should confirm the device they are evaluating meets current standards.

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TABLE 2

Devices that meet standards for home BP measurement

SMBP device suitable for home use	Validation protocol
A&D-767	BHS
A&D-779	International Protocol
A&D-787	International Protocol
OMRON M5-I	International Protocol
OMRON 705IT	International Protocol
OMRON 705 CPII	International Protocol
OMRON MIT	BHS
Microlife 3BTO-A	BHS
Microlife 3AG1	BHS

BHS: British Hypertension Society; International Protocol: European Hypertension Society

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CLINICAL COMMENTARY

Self-measured BP may help us better diagnose and manage hypertension

It has been shown that office blood pressure readings can give false-positive results in those who have "white coat hypertension" and give false-negative readings in those with "white coat normotension" or "masked hypertension"—patients who have normal blood pressure values in the office, but elevated blood pressure values outside the office. This is not a trivial issue. Ten to 20% of patients with normal blood pressure values in the office have elevated blood pressure values throughout the day, and evidence is beginning to mount that the cardiovascular consequences are the same for these patients as for those with sustained hypertension.[1]

The SHEAF trial (and other studies) have thrown another complexity into hypertension control by showing that OBP readings were inaccurate in 22% of treated hypertensive patients—13% had uncontrolled OBP with normal SMBP, and 9% had normal OBP but uncontrolled SMBP.[3]

Thus, SMBP is a potentially very powerful and cost-effective tool that may help us better diagnose and manage this complex disease. I have encouraged my hypertensive patients to do SMBP and, as one who has white-coat hypertension (and a strong family history of hypertension), I am diligent at taking my own SMBP on a regular basis to guard against the insidious onset of this disease.

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What effect do inhaled steroids have on delaying the progression of COPD?

It is imperative for FPs to emphasize the huge benefit of smoking cessation to all COPD patients

EVIDENCE-BASED ANSWER

The annual rate of decline in forced expiratory volume for 1 second (FEV_1) has been researchers' gold standard as an objective measure for progression of chronic obstructive pulmonary disease (COPD). Inhaled corticosteroids (ICS) do not consistently have a statistically significant impact on FEV_1 decline, and thus on the progression of COPD (strength of recommendation [SOR]: **B**, 2 conflicting meta-analyses and numerous conflicting randomized controlled trials). In those studies that did show improvements in FEV_1 decline, the change does not appear to be clinically significant (7.7 to 9.0 mL/year).

These findings do not take into account the potential impact of ICS on such patient oriented outcomes as exacerbation rates, quality of life, outpatient visits, hospitalization, and mortality.

EVIDENCE SUMMARY

No therapies are known to improve long-term lung function in COPD; the goal of disease-moderating therapy is therefore to *slow the rate of decline* compared with the expected rate. All of the studies reviewed used FEV_1 as an objective measure of whether ICS reduce this rate of decline in lung function.

Two recent meta-analyses evaluating medium- to high-dose ICS effects on FEV_1 decline provided conflicting results. One meta-analysis evaluated 8 controlled clinical trials lasting at least 2 years (n=3715) and found that, when compared with placebo, ICS significantly reduced the rate of FEV_1 decline by 7.7 mL/year (P=.02) and that *high-dose* ICS had a greater effect of 9.9 mL/year (P=.01).[1] Another meta-analysis of 6 randomized, placebo-controlled trials with a duration of at least 2 years (n=3571) found a nonsignificant trend in favor of ICS, with a difference in FEV_1 decline of 5.31 mL/year (P=.08) between the ICS and placebo groups.[2]

The differences observed in these 2 meta-analyses may be explained by the authors using slightly different approximations to the standard error, applying slightly different statistical analytical methods, and using different inclusion criteria for trials. However, 5 of the trials in these reviews were the same. Both meta-analyses determined only rate of lung function decline and did not evaluate clinical outcomes.

A trial not included in the previously mentioned meta-analyses evaluated post-bronchodilator FEV_1 decline in 48 patients with *early* signs and symptoms of COPD for 2 years.[3] Subjects were assigned to medium-dose fluticasone propionate or placebo. Early initiation of ICS treatment did not affect the progressive deterioration of lung function as no modifying effect on annual FEV_1 decline was observed, however, the study only had power to detect a 60-mL annual drop in FEV_1.

Meta-analyses and trials evaluating COPD progression have focused on a disease-oriented outcome (the rate of FEV_1 decline). However, patient-oriented outcomes such as exacerbation frequency, hospitalization, health-related quality of life, and mortality might be more important measures of successful therapy. Although such patient-oriented outcomes are not the focus of this review or the included meta-analyses, a few of the small randomized controlled trials included in these meta-analyses suggest that ICS may improve such patient-oriented outcomes. Notably, exacerbation rates significantly decreased by 25% (P=.026), and health status improved (P=.0043) among patients with moderate to severe COPD who were taking fluticasone compared with those taking placebo.[4]

CONTINUED

Inhaled corticosteroids do not consistently have an impact on delaying the progression of COPD

In mild to moderate COPD, patients treated with triamcinolone had fewer respiratory symptoms (P=.005), fewer visits to a physician because of respiratory illness (P=.003), and improved airway reactivity (P=.02).[5] Some systematic reviews and other randomized trials suggest that ICS have significant benefit on these patient outcomes.[6]

RECOMMENDATIONS FROM OTHERS

Scientists from the National Heart, Lung, and Blood Institute and the World Health Organization provided an update of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in 2003.[7] They reported that regular treatment with ICS does not modify the long-term decline of FEV_1 in patients with COPD. However, they recommended treatment with ICS for symptomatic COPD patients with an FEV_1 less than 50% of predicted (stage III: severe COPD and stage IV: very severe COPD) and repeated exacerbations (ie, 3 in the last 3 years). Guidelines from other countries also suggest that ICS do not affect the progression of COPD, but support the use of ICS for patients with severe COPD and repeated exacerbations.[8–10]

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CLINICAL COMMENTARY

Smoking cessation a huge benefit to all COPD patients

In adults aged more than 30 years old with COPD, the physiological abnormality is primarily an accelerated decline in the FEV_1 from the normal rate of about 30 mL per year to nearly 60 mL per year. In patients with COPD, smoking cessation is the only proven means to slow down the progression of the disease, with up to a sustained 50% reduction in the rate of lung-function decline.

Therefore, it is imperative for family physicians to underscore the magnitude of the benefit of smoking cessation to all COPD patients and to emphasize the current evidence that inhaled corticosteroid has a limited impact in delaying the progression of the disease.

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How effective is prophylactic therapy for gout in people with prior attacks?

EVIDENCE-BASED ANSWER

Colchicine (strength of recommendation [SOR]: **B**, based on 1 double-blind crossover study), allopurinol (SOR: **B**, based on 2 cohort studies), and weight loss (SOR: **B**, based on 1 small cohort study) have been shown to reduce symptomatic recurrences of gout, although the data to support their use is limited. Some evidence suggests that despite their serum uric acid–lowering effects, uricosurics (such as probenecid) fail to reduce gout attacks (SOR: **B**, based on 2 cohort studies). We were unable to find any double-blind, placebo-controlled long-term outcome studies addressing this problem.

EVIDENCE SUMMARY

The majority of gout sufferers are uric acid undersecretors rather than overproducers; however, many patients will have a combination of these 2 processes, as well as caloric or purine overindulgence. Efforts to limit the frequency and intensity of gout attacks have focused on reducing the uric acid load or reducing the inflammatory response to intra-articular crystal deposition. Pharmacologic therapies include 1) uricosurics, such as probenecid, sulfinpyrazone and benzbromarone (used mostly in Europe), which increase the renal clearance of uric acid, 2) xanthine oxidase inhibitors such as allopurinol, which limit the formation of uric acid to yield a more water soluble chemical, and 3) anti-inflammatory medications, including nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine. Obesity and insulin resistance are associated with elevated uric acid, suggesting that weight loss may also help reduce episodes of gout.

A double-blinded crossover study of 38 veteran men with recurrent gout found that the addition of daily colchicine to uricosurics reduced the frequency of attacks by nearly two thirds in 6 months of follow-up.[1] A cohort study of 208 men with confirmed gout who used either daily colchicine alone or colchicine with uricosurics for 2 to 10 years found marked improvements in attack frequency in both groups, yet there was no difference between the intervention groups.[2] An additional study followed 734 patients (including some of the subjects in the first cohort study) and reported similar outcomes.[3]

Allopurinol was studied in 46 patients using prophylactic colchicine with an average follow-up of 12 months.[4] Attack rates were unchanged for the first several weeks followed by a decline in the attack rate and a regression of tophi. When allopurinol was added to uricosurics in 48 patients, tophi were reduced.[5]

An average weight loss of 7.7 kg had a beneficial effect on serum uric acid levels and gout attack rates in 13 nondiabetic men, who were placed on a carefully controlled 1600-calorie diet with 40% of calories from complex carbohydrates.[6]

In a small study, the addition of uricosurics did not reduce the gout attack rate in 14 patients with nontophaceous gout.[7] Patients were followed over 12 to 15 months in a crossover study of colchicine and placebo versus colchicine and sulfinpyrazone. Although this study had limited power, a larger cohort study had similar findings over a longer follow-up period.[3]

We were unable to find any applicable studies of daily NSAID use, dietary purine control, or alcohol reduction for the secondary prevention of gout. A prospective study of primary gout involving 47,150 men followed over 12 years noted a relative risk (RR) of gout 1.41 (95% confidence interval [CI], 1.07–1.86) in the highest quintile of meat eaters, a RR of 1.51 (95% CI, 1.17–1.95) in the highest quintile of seafood eaters, and an inverse relationship of dairy intake with gout risk.[8] Thiazide diuretics appear to increase the likelihood of a gout diag-

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nosis and if used, could be discontinued, although no studies have investigated this intervention. Most of the gout studies were performed in the 1960s using simple cohort designs and limited statistical analysis; some used combinations of medications and variable dosing. Only allopurinol appears effective in resorbing tophi[5] and may have greater utility for patients with severe tophaceous gout, in those intolerant to uricosurics, in gross overproduction of uric acid, for patients with uric acid stones, or for those with renal impairment.

RECOMMENDATIONS FROM OTHERS

An expert panel, recruited by the Agency for Healthcare Research and Quality, recently published a summary combining evidence and expert opinion, which suggested that colchicine is a good prophylactic therapy and that uric acid lowering drugs (allopurinol, probenecid, and sulfinpyrazone) are effective in decreasing attack frequency in those with more than 2 attacks per year.[9] Weight loss and alcohol reduction were also encouraged. A Cochrane review of this topic is scheduled for completion in 2004.

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CLINICAL COMMENTARY

Prophylactic therapy is recommended for frequent attacks

Long-term therapy is recommended when frequent gouty attacks occur. Care is warranted in the use of colchicine with erythromycin, simvastatin, and cyclosporine, since these drugs modify the excretion of colchicine, which may lead to toxic doses.[10] Uric acid–lowering agents, such as allopurinol and probenecid, should be avoided in acute attacks of gout, due to potential worsening of inflammation.

Nonadherence with long-term prophylactic therapy for gout can lead to acute attacks, but patients who adhere to prophylactic therapy can still experience occasional acute breakthroughs of gout. The Cochrane review in progress may shed more insight into the prevention of acute gouty inflammation..

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Does tight control of blood glucose in pregnant women with diabetes improve neonatal outcomes?

EVIDENCE-BASED ANSWER

In pregnant women with preexisting type 1 diabetes mellitus, maintaining near-normal blood glucose levels decreases the rate of major congenital anomalies (defined as those causing death or a serious handicap necessitating surgical correction or medical treatment). Prolonged preconception control of blood sugar to near-

normal levels reduces the rate of major congenital anomalies close to those seen in women without diabetes (strength of recommendation [SOR]: **A**, based on prospective cohort studies and randomized controlled trial [RCT]).

Intensive management reduces the risk of congenital anomalies more than conventional therapy, and lowers the risk of neonatal hypoglycemia (SOR: **B**, based on RCT). Very tight control does not reduce clinically significant neonatal morbidity but does increase the risk of maternal hypoglycemia (SOR: **B**, based on a systematic review). Evidence is insufficient about whether or not these statements hold true for women with type 2 diabetes.

In women with impaired glucose tolerance, dietary control reduces neonatal hypoglycemia. To date, studies have not found statistically significant reductions in admission rates to the special care nursery or birth weights above the 90th percentile (SOR: **B**, systematic review). Evidence is insufficient to suggest improved outcomes with therapy in women with gestational diabetes. Standard recommendations typically recommend tight control in this population as well.

EVIDENCE SUMMARY

Two studies show that in type 1 diabetes mellitus, elevated blood glucose levels in early pregnancy (HbA_{1c}=6%–8%) are associated with a threefold increase in fetal malformations.[1,2] Maintaining preconception and early pregnancy blood glucose levels in the normal range can reduce this risk. A meta-analysis comparing 16 studies of women with pregestational diabetes—13 of which included only women with type 1 diabetes—found that women receiving preconception care had lower early first trimester HbA_{1c} levels than those who did not (7.9% vs 9.6%) and delivered fewer infants with major congenital anomalies (relative risk [RR]=0.36; 95% confidence interval [CI], 0.22–0.59).[2] One limitation of this study was that preconception care was not consistently defined among the included studies.

For women with impaired glucose tolerence, dietary control reduces neonatal hypoglycemia

A 10-year RCT evaluated the outcomes of 270 pregnancies in women who had received either intensive (SQ infusion or multiple daily injections) or conventional insulin regimens prior to pregnancy. Women were advised to use intensive therapy when they were trying to conceive, and all were changed to intensive therapy if pregnancy was confirmed. Women in the intensive therapy group had normal HbA_{1c} levels for an average of 40 months before conception. Women receiving intensive therapy had lower mean HbA_{1c} levels at conception (7.4 ± 1.3 SD vs 8.1 ± 1.7 SD) and fewer major congenital anomalies (0.7% vs 5.9%; number needed to treat=19) than did women in the conventional group. When infants with genetic malformations were excluded from the analysis, rates of congenital malformations were similar in women switched to intensive therapy either before or after conception (3.8% vs 3.6%). No differences were seen between neonatal mortality, spontaneous abortion rates, birth weights, Apgar scores, and hypocalcemia or hypoglycemia rates.[3]

When tight and very tight control of glucose in pregnant women with pregestational diabetes were compared in a Cochrane systematic review, rates of maternal hypoglycemia in the very tightly controlled group were higher (odds ratio [OR]=25.96; 95% CI, 4.91–137.26).[5] An RCT of 118 women with pregestational diabetes compared 4-times-daily vs twice-daily doses of insulin. Infants born to women receiving 4-times-daily insulin had significantly lower rates of neonatal hypoglycemia (RR=0.17; 95% CI, 0.04–0.74). While the trend was toward improved neonatal metabolic effects in the trials, the clinical significance of these findings is not clear.

For women with gestational diabetes not controlled by diet, ACOG recommends adding insulin therapy

Whether or not treatment of gestational diabetes improves outcomes is uncertain. A Cochrane systematic review evaluating a small number of trials, with variable quality and inconsistent outcome measures, compared dietary management to routine care in gestational diabetics. While fewer infants with birth weights >4000 g were delivered in the diet therapy group (OR=0.78; 95% CI, 0.45–1.35), the results were not statistically significant. No other important clinical differences were found.[6]

Another Cochrane systematic review evaluated the effects of dietary treatment of women with impaired glucose tolerance and gestational diabetes. Three trials with a total of 223 women with impaired glucose tolerance found a significant reduction in the rate of neonatal hypoglycemia (RR=0.25; 95% CI, 0.07–0.86). There was no significant change in the rates of cesarean section (RR=0.86; 95% CI, 0.51–1.45), admission to the special care nursery (RR=0.49; 95% CI, 0.19–1.24), or birth weights greater than the 90th percentile (RR=0.55; 95% CI, 0.19–1.61). Inadequate power may well account for the failure to reach significance in these outcomes.[7]

RECOMMENDATIONS FROM OTHERS

The American College of Obstetrics and Gynecology (ACOG) recommends that women with pregestational diabetes maintain fasting plasma glucose levels between 60–90 mg/dL and 2-hour postprandial levels <120 mg/dL.[8] For women with gestational diabetes who are not controlled within these targets on dietary therapy alone, ACOG recommends the addition of insulin therapy.[9]

The American Diabetes Association recommends that women with pregestational diabetes maintain capillary plasma glucose levels of 80–110 mg/dL before and <155 mg/dL 2 hours after meals before pregnancy and while trying to conceive.[10] The ADA does not list target glucose levels for women with pregestational diabetes once they become pregnant. The ADA recommends the use of diet and insulin therapy to maintain preprandial plasma glucose levels of <105 mg/dL and 2-hour postprandial levels below <130 mg/dL in gestational diabetes.[11]

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CLINICAL COMMENTARY

Glucose control makes a difference for pregnancy outcomes in type I diabetes

It is well accepted that glucose control makes a difference for pregnancy outcomes in women with type 1 diabetes. Since similar studies have not been done in women with preexisting type 2 diabetes, we have to assume that the risk is also high for them. Preconception counseling about glucose control is so important for women with diabetes. Fortunately, because they generally have routine visits for their chronic care, we have an opportunity to initiate discussion of glucose control in relationship to pregnancy planning. Routine diabetes care visits also give us the opportunity to discuss other important preconception topics.

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DRUG BRAND NAMES

Allopurinol • Lopurin, Zyloprim
Amitriptyline • Elavil, Endep
Benzbromarone • Urinorm
Botulinim toxin A • Botox
Clindamycin • Cleocin
Fluoxetine • Prozac
Fluticasone • Flovent
Gabapentin • Neurontin
Metronidazole (intravaginal) • MetroGel
Probenecid • Benemid, Probalan
Sumatriptan • Imitrex
Tizanidine • Zanaflex
Triamcinolone • Azmacort
Valproate • Depacon