decreased libido in the first year of use. In a 1-year study of terazosin (an alpha-blocker), finasteride, both drugs, or placebo, terazosin modestly improved AUA symptom scores, while finasteride was no better than placebo.[1] Alpha-blockers are less expensive than finasteride and reach their maximum effect in 4 to 6 weeks. In contrast, it may take months for patients taking finasteride to perceive any effect and years to see the maximum benefit. Alpha-blockers are therefore a better first choice for the medical treatment of BPH. For patients with palpably enlarged prostates and moderate to severe symptoms who do not respond to an alpha-blocker, finasteride may offer an alternative to surgery. Patients should be informed of the length of time necessary to notice an improvement and the possibilities of decreased libido and impotence.

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REFERENCE

1. Lepor H, Williford WO, Barry MJ, et al. The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. N Engl J Med 1996; 335:533-9.

Potentiation of Warfarin by Acetaminophen

Hyiek EM, Heiman H, Skates SJ, Sheehan MA, Singer DE. Acetaminophen and other risk factors for excessive warfarin anticoagulation. JAMA 1998; 279:657-62.

Clinical question **Can the anticoagulant effect of warfarin be potentiated by the concurrent use of acetaminophen (Tylenol)?**

Background Warfarin anticoagulation is used in many patients at increased risk for thromboembolic events. Hemorrhagic complications are more common as the international normalized ratio (INR) increases above 3.0. Minimal information is available on causes of very high INR levels (>6.0) in clinical practice.

Population studied Patients who had been taking warfarin for more than 1 month with a target INR between 2.0 and 3.0 were identified from an outpatient anticoagulant therapy unit. Case patients had an INR >6.0 and controls had an INR between 1.7 and 3.3. In both the case and control groups the mean age was 70 years, approximately 50% were women, and nearly all were white. Conditions leading to anticoagulation did not differ between groups. For most cases, their high INR value represented a recent deterioration (<1 month) in control of anticoagulation. All of the case patients and controls had started taking acetaminophen since their previous INR.

Study design and validity Case patients with an INR >6.0 during the study period were identified from daily INR logs. Controls were randomly selected during the same period from patients with INR between 1.7 and 3.3. All subjects were contacted by phone within 24 hours of their blood draw and questioned about recent medication use, dose change, diet, illness, alcohol consumption, and warfarin compliance. Patients were not specifically informed of their INR value or the true purpose of the study. Half of the cases had previously been informed of their abnormal result through the usual clinic mechanisms. It is not clear if the interviewers were blinded to the patients' INR value.

This case-control study design is appropriate given the infrequent occurrence of cases. This method is, however, susceptible to more bias than randomized controlled trials or cohort studies. In the research business, this type of study is known as a "fishing expedition," an exploratory study designed to find possible links that need further study with more rigorous methods. The finding of a dose-response relationship in the interaction between acetaminophen and warfarin and the fact that this effect has been reported in other studies adds credence to this study's results.

Outcomes measured Outcomes measured included medication use, recent diet, illness, alcohol consumption, and actual warfarin use. Other patient-oriented outcomes, including significant hemorrhage and death, were not studied.

Results A total of 111 case patients were identified and 93 of these were interviewed. An additional 279 controls were identified, of which 196 were interviewed. Cases and controls did not differ in terms of age, sex, race, indication for anticoagulation, length of warfarin therapy, dosage of warfarin, or INR value preceding the study period. A dose-response relationship was found between more than 7 tablets per week of acetaminophen and an increased risk for an INR >6.0. If the dose of acetaminophen was greater than 28 pills per week, the risk of having an INR >6.0 was 10-fold higher than controls (OR = 10.0; 95% CI, 2.6 - 37.9). Other risk factors independently associated with an elevated INR included taking a new medication known to potentiate warfarin, taking more warfarin than prescribed, diarrhea, advanced malignancy, and decreased oral intake. Intake of foods rich in vitamin K and moderate alcohol intake appeared to be moderately protective.

Recommendations for clinical practice **This study presents compelling data that point to acetaminophen (Tylenol) intake as a risk factor for elevations of INR levels in patients taking warfarin. Occasional intake did not confer risk, but patients**

taking more than 7 tablets of regular strength (325 mg) acetaminophen per week should be monitored closely for any rise in INR levels. Patients taking warfarin who experience a sudden jump in their INR levels should be queried regarding recent acetaminophen use. Steady intake of foods containing vitamin K and moderate alcohol consumption (up to 2 drinks per day) may protect patients from INR elevations.

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Warming Bupivacaine for Intradermal Anesthesia

Jones JS, Plzak C, Wynn BN, Martin S. Effect of temperature and pH adjustment of bupivacaine for intradermal anesthesia. Am J Emerg Med 1998;16:117-120.

Clinical question What effect does the warming and buffering of bupivacaine (Marcaine) have on the pain associated with intradermal injection and the onset of anesthesia?

Background Despite bupivacaine's long duration of action, other local anesthetics are more often used for intradermal anesthesia because of bupivacaine's tendency to cause burning with injection and to have a prolonged onset of anesthesia. Buffering the bupivacaine has been shown to decrease the pain of infiltration. Whether warming bupivacaine to body temperature can reduce injection-associated pain and the duration of onset of anesthesia is unknown.

Population studied The population studied included 40 healthy adult volunteers from the medical and nursing staff at Butterworth Hospital in Grand Rapids, Michigan. There were no reported dropouts and no biographical data were given.

Study design and validity This 3-part randomized, double-blind study compared bilateral forearm injection of room temperature 0.5% bupivacaine buffered to a pH of 7.1 with 8.4% sodium bicarbonate with each of the following three solutions: buffered bupivacaine warmed to 37°C; unbuffered bupivacaine at 37°C; and unbuffered bupivacaine at room temperature. Comparison injections occurred over a 1-month time period. Volunteers rated their pain at the site of injection on a scale of 0 to 100. Participants were given guidelines for the pain scale to create some consistency in rating. Duration of onset of anesthesia in a 1-cm diameter was timed with a stopwatch. The methods for warming and buffering the solution were carefully defined.

Outcomes measured Mean injection pain scores and the duration of onset of anesthesia were compared between buffered room temperature bupivacaine and the other three solutions.

Results Warming buffered bupivacaine significantly reduced the pain of injection by a mean score of 12.1 mm (95% CI, 6.9 - 16.4). Warming also reduced the time of onset of anesthesia by 12.1 seconds from a mean latency time of 83.7 seconds to 71.6 seconds ($P = 0.03$; 95% CI, 0.6 - 23.6). Buffering room temperature bupivacaine reduced the mean pain score compared with an unbuffered solution by 12.8 mm (95% CI, 7.7 - 17.0). Buffering did not, however, affect the duration of onset of anesthesia (95% CI, -13.4 to 10.4 sec). Warming had more of an effect on pain than buffering, but both appeared to have a cumulative effect.

Recommendations for clinical practice **Warming and buffering bupivacaine decreases the pain of injection on intact nontraumatized skin. Although it is feasible to buffer bupivacaine in most clinical settings, it may be difficult to warm the solution as was done in this study. Warming bupivacaine reduced the time of onset of anesthesia statistically, but this difference is unlikely to be clinically significant. Before adopting the practice of warming bupivacaine, which may be more technically challenging than buffering, further studies should be performed on traumatized tissue to see if the results are consistent. A recent study has shown that slower rates of lidocaine infusion can reduce the pain of injection.[1] Thus, paying attention to the speed of injection of bupivicaine may also be important.**

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REFERENCE

1. Schooff M. Lessening the pain of lidocaine injection. J Fam Pract 1998; 46:279.

Lack of Efficacy of Cisapride and Nizatidine in Dyspepsia

Hansen JM, Bytzer P, Schaffalitzky de Muckadell OB. Placebo-controlled trial of cisapride and nizatidine in unselected patients with functional dyspepsia. Am J Gastroenterol 1998; 93:368-74.

Clinical question **Are cisapride or nizatidine useful for the treatment of nonulcer dyspepsia in primary care patients?**

Background While many physicians empirically treat nonulcer dyspepsia with an H_2-antagonist, several small trials have not shown these agents to be effective. Others believe that nonulcer dyspepsia is a motility dis-