The HelpDesk Search Strategy

HelpDesk Answers are intended to provide the same quality response to a clinical question as would be achieved by a search-savvy physician spending an hour or so on the Internet. Authors of HelpDesk Answers are required to search PrimeEvidence (http://www.primeanswers.org) and the TRIP database (www.tripdatabase.com). These portals provide access to more than a dozen sources of the highest quality evidence-based clinical information, including BMJ Clinical Evidence, the Guide to Clinical Preventive Services, AHRQ Evidence Reports, and others. Searches of the Cochrane Database, Medline, and other databases are also included, as needed.

What antiepileptic drugs cause elevation of liver transaminases?

Evidence-Based Answer

Essentially all antiepileptic medications can raise liver enzymes or cause hepatoxicity as a rare side effect; "periodic" liver enzyme monitoring is recommended. (SOR **C**, based on expert opinion.) However, valproate and felbamate are associated with higher rates of hepatic failure (SOR **B**, based on cohort studies) and have specific liver function monitoring recommendations.

A recent systematic narrative review concluded that adverse hepatic events can occur with any antiepileptic drug; these effects may range from mild elevations in liver enzymes to rare cases of hepatitis or liver failure.[1] Unfortunately, severe hepatotoxicity can occur after repeatedly normal liver function measurements. Consequently, baseline and periodic liver enzyme monitoring was recommended.

With the exception of felbamate, second-generation antiepileptic medications (eg, gabapentin, lamotrigine, topiramate, levetiracetam, oxcarbazepine, zonisamide) generally have a decreased incidence of hepatic enzyme elevations compared with older medications (eg, phenobarbital, phenytoin, carbamazepine, valproate).[1]

In an investigation conducted by the World Health Organization, valproate was the third most common drug associated with liver injury.[2] A total of 37 fatalities due to hepatic failure were attributed to valproate use in the United States between 1978 and 1988. For individuals receiving valproate monotherapy, the calculated fatality rate was 1 in 37,000.[3] The risk of hepatotoxicity is greatest among children younger than 2 years, and valproate use is contraindicated for patients with preexisting liver disease or significant hepatic dysfunction.[4] The FDA black box warning for valproate recommends performing pretreatment liver function tests and frequent monitoring throughout therapy, particularly within the first 6 months.

Hepatotoxicity with felbamate was reported at an incidence of 1 in 10,000 patients.[5] Felbamate is currently not considered a first-line agent for epilepsy, but remains on the market with an FDA black box warning for hepatic failure. The manufacturer recommends written consent be obtained prior to beginning therapy, and that liver function tests be monitored throughout therapy.

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3. Dreifuss FE, Santilli N, Langer DH, Sweeney KP, Moline KA, Menander KB. Valproic acid hepatic fatalities: a retrospective review. *Neurology* 1987; 37:379–385. **[LOE 1a]**
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In adolescent females with primary dysmenorrhea, are oral contraceptive agents as effective as nonsteroidal anti-inflammatory drugs (NSAIDs) for reducing abdominal pain?

Evidence-Based Answer

The answer is unknown at present. No head-to-head trials comparing oral contraceptives with NSAIDs for the relief of dysmenorrhea could be located.

NSAIDs have been the mainstay of therapy for dysmenorrhea since the 1970s. In a large systematic review of the literature, naproxen, ibuprofen, mefenamic acid, and aspirin were all effective treatments for primary dysmenorrhea. Ibuprofen was found to have the most favorable risk-to-benefit ratio.[1] However, other reviewers have

concluded that there is no evidence of an improved side-effect profile for 1 of these NSAIDs versus another.[2]

A literature search in 2001 identified no randomized controlled trials (RCTs) testing the efficacy of low-dose combined oral contraceptives in the treatment of primary dysmenorrhea.[3] Subsequently, a double-blind RCT of 76 adolescents treated with an oral contraceptive or placebo for menstrual symptoms found that the combined oral contraceptive was more effective than placebo (mean difference 2.7 points on the Moos Menstrual Distress Questionnaire; 95% CI, 0.88–4.53).[4] However, this study allowed research participants to take NSAIDs in conjunction with oral contraceptive agents, blurring the results. The study did cite other possible benefits of oral contraceptive agents, including improvement in acne and dysfunctional uterine bleeding, and pregnancy prevention.

No RCTs were identified that directly compared oral contraceptive agents with NSAIDs for primary dysmenorrhea.

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2. Marjoribanks J, Proctor ML, Farquhar C. Nonsteroidal anti-inflammatory drugs for primary dysmenorrhoea. *Cochrane Database Syst Rev* 2003; (4): CD001751. **[LOE 1a]**
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Is too much vitamin E dangerous?

Evidence-Based Answer

Recent evidence suggests a very modest but statistically significant increase in all-cause mortality with supplemental intake of vitamin E ≥400 IU/day. (SOR **A**, based on meta-analyses.)

Vitamin E is a popular dietary supplement in the United States, especially among older men concerned about risk of heart disease or prostate cancer. The most commonly used supplement dose is 400 IU/day. This amount is far higher than the recommended dietary allowance (RDA), but still well below the current Institute of Medicine (IOM) safe upper intake level (**TABLE**).

TABLE

Ranges of vitamin E intake

Average daily US dietary intake*	6–8 IU
USDA recommended dietary allowance*	15 IU
Typical multivitamin product	30 IU
100% daily value (as shown on product labels)	30 IU
Commonly available vitamin E supplements	200, 400, 1,000 IU
IOM tolerable upper intake level*	1,000 mg†

*Source: Institute of Medicine. Vitamin E. In: Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, DC: National Academies Press; 2000:186–283.[1]
†Equals 1,000 IU of synthetic vitamin E or 1,500 IU of natural vitamin E.
IOM=Institute of Medicine; USDA=United States Department of Agriculture.

In the early 1990s, major epidemiological studies such as The Nurses' Health Study and The Physicians' Health Study reported a 20% to 40% reduction in cardiovascular deaths for enrollees who used vitamin E supplements. However, 2 recent meta-analyses of multiyear intervention trials both concluded that there was little to no cardiovascular benefit and a modest increase in all-cause mortality.[2,3]

A meta-analysis divided 19 randomized controlled trials with 135,967 participants into low dose and high dose using 400 IU as the dividing point and reported on all-cause mortality. The study reported a nonsignificant trend toward reduced mortality (risk ratio [RR] 0.98; 95% CI, 0.96–1.01) with low doses and a modestly increased risk (RR 1.04; 95% CI, 1.01–1.07) with high doses.[2] The supplement industry organization, Council for Responsible Nutrition (www.crnusa.org), has posted fact sheets (eg, http://www.crnusa.org/pdfs/CRN_VitaminE_FactSheet1104.pdf) on its web site critiquing the methods of the study, the main point being that most of the high-dose (900–2,000 IU/day) trials included people already diagnosed with various diseases at enrollment, and thus the results are not necessarily relevant for healthy people.

A more recent meta-analysis included 68 randomized but not necessarily controlled clinical trials of various antioxidants encompassing 232,606 subjects. Trials included beta-carotene, vitamin A, vitamin C, vitamin E, selenium, and combinations. Analysis for vitamin E showed that either singly