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St John's Wort and Drug Interactions

Source: Markowitz JS, et al. *JAMA*. 2003;290:1500-1504.

THE CYTOCHROME P450 SYSTEM IS responsible for the metabolism of the majority of currently prescribed medications. The 2 most common P450 pathways involved in drug metabolism are CYP 3A4 and 2D6, which together are responsible for metabolizing almost three quarters of currently available medications. Any agent that either blocks or enhances either of these enzyme pathways can potentially induce medication toxicity (through drug accumulation) or reduce drug efficacy (through more rapid metabolic disposal).

St. John's Wort (SJW) is a popular over-the-counter agent used for depres- sion, the active ingredient of which is felt to be hypericum. Case reports have suggested that SJW might affect drugs as diverse as cyclosporine, indinavir, tricyclic antidepressants, simvastatin, and even oral contraceptives. For instance, it has been suggested that the enhanced activation of the CYP3A4 system by SJW might lead to increased metabolism of ethinyl estradiol in oral contraceptives, leading to unplanned pregnancy.

Markowitz and associates studied pharmacokinetics of substances metabolized by the 3A4 and 2D6 CYP systems when coadministered with SJW. A 2-fold increase in 3A4 activity was seen, but no effect upon 2D6 was found. Since many drugs are metabolized by the CYP 3A4 system, clini- cians must recognize which patients are taking SJW to minimize adverse effects upon medication pharmacokinetics. ■

Serum Potassium and Stroke Risk Among Hypertensive Adults

Source: Smith NL, et al. *Am J Hypertens*. 2003;16:806-813.

OBSERVATIONAL DATA INDICATE THAT persons who consume greater levels of dietary potassium have both lowered blood pressure and reduced risk of stroke. This protective effect of dietary potassium intake is seen in both hypertensive and normotensive persons, though it is more pronounced in men than women. In some hypertension trials, serum potassium levels have shown an inverse relationship with stroke, but of course many of these subjects received diuretic therapy with an anticipatable decline in serum potassium, and these findings have not been consistent among all populations.

Using data from the Group Health Cooperative observational study (a Washington state-based HMO), Smith and colleagues evaluated the relationship between hypokalemia and subsequent ischemic (n = 593) or hemorrhagic stroke (n = 125) in this population of hypertensive adults compared to controls (n = 2397). Potassium status was defined by traditional levels of hypokalemia (potassium < 3.5) measured in the year prior to stroke.

Hypokalemia was associated with substantial increases in risk of stroke, both for ischemic (odds ratio, 2.04) and hemorrhagic (odds ratio, 3.29) stroke. Since no gradient of stroke risk through the normal range of potassium was discerned, the likelihood that it is indeed the hypokalemia that is etiologically related to stroke risk is further strength- ened. Use or non-use of diuretics did not affect the relationship between hypokalemia and stroke. The mechanism by which hypokalemia might aggravate stroke risk is uncertain. ■

Skin Cancer Prevention and Detection Practices Among Siblings of Patients with Melanoma

Source: Geller AC, et al. *J Am Acad Dermatol*. 2003;49:631-638.

MORE THAN ONE-HALF MILLION Americans have invasive malignant melanoma (MEL), and the incidence of this disorder has risen an alarming 15-fold since World War II. Family members (first degree) of persons with MEL have as much as a 2-8- fold increased risk of developing MEL.

Recommendations by such agencies as the United States Preventive Services Task Force and the National Institute of Health include the suggestion that family members of patients with MEL should be provided skin cancer screening, risk education, and reduction of ultraviolet radiation exposure. When surveillance for MEL is carried out amongs family members, the stage at which MEL is discovered is earlier than that of the index case. Whether such recommendations are adequately used has not been studied.

Geller and associates contacted 585 siblings of 278 persons diagnosed with MEL within the previous 2 months. Although most of the siblings (62%) had examined their skin in the past year, only slightly more than half used sunscreen with at least SPF 15, and only

27% had received a skin cancer examination by a dermatologist. The message to family members of MEL victims about positive steps to maintain their own cutaneous health requires greater advocacy. ■

TZDs and HF in People with Type 2 Diabetes

Source: Delea TE, et al. *Diabetes Care*. 2003;26:2983-2989.

THIAZOLIDINEDIONES (TZDS) OFFER numerous potential benefits in diabetic patients, including improved insulin-stimulated glucose disposal, decreased insulin resistance, and favorable lipid effects. One of the well-recognized adverse effects of TZDs is an increase in plasma volume, reflected by a decrease in hematocrit, weight gain, and edema. Although case reports of an association between TZDs and heart failure have been reported, no published study has specifically examined this issue.

Relying on a large health insurance claims database, Delea and colleagues compared data from type 2 diabetic patients receiving TZDs (n = 5441) with control subjects (n = 28,103) based upon observational data accrued August 1997-March 2001.

During the follow-up period, subjects receiving TZDs were more than 1½ times more likely to experience heart failure than control subjects (2.3% incidence vs 1.4%). This translates into an approximately 60% greater relative risk of heart failure for diabetics treated with TZDs than controls. On the other hand, having received a prescription for metformin in the 3 months before initiation of the observation period was associated with a lesser risk of heart failure, hence "antidiabetic treatment" per se cannot be held culpable.

Previous warnings have cautioned specifically about the combination of insulin with TZDs, indicating an increased risk of heart failure; in this study, however, no discernible difference in risk of heart failure between TZDs with, or without, insulin was seen. ■

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Exercise Plus Behavioral Management in Patients with AD

Source: Teri L, et al. *JAMA*. 2003; 290:2015-2022.

ALTHOUGH ALZHEIMER'S DISEASE (AD) prompts clinicians to immediately address cognitive function, there is much less awareness of AD effect upon physical conditioning. AD patients have been found to be at greater risk of falls, fractures, rapid decline in mobility, and undernutrition. Pilot studies of exercise programs for AD patients have been promising, with benefits extending beyond simple conditioning to include favorable effects upon depression.

Home-based caregivers, for whom little guidance has been available about optimum techniques for exercise and behavioral management, provide much of the care for AD. This study randomized AD patients (n = 153) to traditional community care or an active exercise and behavioral management program. The active treatment group (patient and caregiver) received 12 sessions lasting 1 hour with instruction about exercise, strength training, balance, and flexibility, with a goal of at least 30 minutes of moderate intensity exercise daily. Supervised instruction occurred for 3 months, after which the patient and caregiver were "on their own"' for an additional 24 months.

When compared to persons who received "routine" care, at 3 months time there was a significant difference in the SF-36 (quality of life evaluation) and depression scores in favor of active treatment. Indeed, while improvements in scores were seen amongst the active treatment group, declines in scores were seen for traditional care. At 24 months, there were still significant differences between the 2 groups. Teri et al conclude that the robust and enduring benefits of a simple exercise program, when coupled with behavioral management skills for caregivers, are achievable for AD patients and merit consideration by clinicians. ■

Spironolactone in Resistant HBP

Source: Nishizaka MK, et al. *Am J Hypertens*. 2003;16:925-930.

A COMMONLY ACCEPTED DEFINITION of resistant hypertension (r-HTN) is failure to obtain blood pressure control (ie, < 140/90) with 3 or more different classes of antihypertensive medication. As many as 30% of hypertensive patients may fall into this category; for instance, in the recently completed ALLHAT trial, 34% of subjects, despite intensive multidrug treatment, failed to achieve goal BP.

In the past, use of aldosterone antagonists like spironolactone (SPL) was often reserved for cases of aldosteronism, or in persons plagued with persistent hypokalemia. Doses that may lead to an unacceptable adverse effect profile (100-400 mg/d) were not uncommonly used in such circumstance. Whether more modest doses of SPL (12.5-50 mg/d) might prove effective in r-HTN was the subject of this study.

At 6 months of treatment with SPL, the mean reduction in BP was 25/12 mm Hg. Although subjects who ultimately were determined to have aldosteronism required a higher dose of SPL than persons with low plasma renin, there was no statistically significant difference in efficacy between these subgroups. Similarly, there was no white vs black ethnic disparity in efficacy. The adverse effects profile included 4% incidence of breast tenderness, 7% incidence of worsening renal function, and 3% incidence of hyperkalemia.

It is encouraging that an inexpensive medication (available generically) is generally well tolerated and can provide substantial improvements in BP for persons already on multidrug therapy. ■