

Drug Overdosing: How to Avoid Medication Side Effects

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## ABSTRACTS

Physicians' Desk Reference.

Physicians' Desk Reference.

2003; 57th Edition

AMA Drug Evaluations, Annual 1994. : .

AMA.

1994;

AMA Drug Evaluations.

AMA.

1994;

Code of Medical Ethics.

American Medical Association Council on Ethical and Judicial Affairs.

1999; 1998-1999 Edition.

Is academic medicine for sale?

Angell M.

*N Engl J Med.* 2000; 342(151-68)

Prescription for profit.

Angell MRAS.

*The Washington Post.* 2001.Jun.20:A27.

Inhaled steroids for asthma cause bone loss, study finds.

Associated Press.

*San Diego Union-Tribune.* 2001.Sep.27:A14.

The prescription as final common pathway.

Avorn J.

*Int J Technol Assess Health Care.* 1995; 11(3):384-90.

There is an informational void about pharmaceuticals in the training of most doctors, despite the importance of the prescription in medical care. The writing of the prescription is the final common pathway in therapeutic decision making, which involves such diverse forces and disciplines as anthropology, decision science, health economics, ethics, and politics, as well as pharmacology and clinical medicine. Programs to improve the precision and cost-effectiveness of doctors' prescribing must consider all of these factors if pharmacotherapeutics are to be used optimally

Adverse cardiovascular events associated with the use of Viagra.

Azarbal BMJSPKCBKS.

2000.Mar.14; 35(Suppl. A 553A554A;)

A brief review paper of the efficacy and safety of atorvastatin in early clinical trials.

Bakker-Arkema RG, Best J, Fayyad R, et al.

*Atherosclerosis*. 1997 May; 131(1):17-23.

Preclinical and clinical data on atorvastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, indicate that it has superior activity in treating a variety of dyslipidemic disorders characterized by elevations in low-density lipoprotein cholesterol (LDL-C) and/or triglycerides. Results for patients randomized in early efficacy and safety studies were combined in one database and analyzed. This analysis included a total of 231 atorvastatin-treated patients (131 with hypercholesterolemia (HC), 63 with combined hyperlipidemia (CH), 36 with hypertriglyceridemia (HTG), and 1 with hyperchylomicronemia (Fredrickson Type V)). Patients were treated with a cholesterol-lowering diet (National Institutes of Health National Cholesterol Education Program Step 1 diet or a more rigorous diet) and either 2.5, 5, 10, 20, 40, or 80 mg/day of atorvastatin or placebo. Efficacy was based on percent change from baseline in total cholesterol, total triglycerides, LDL-C, very low-density lipoprotein cholesterol (VLDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein B (apo B), and non-HDL-C/HDL-C. Safety was assessed in all randomized patients. Atorvastatin seemed to preferentially lower those lipid and lipoprotein component(s) most elevated within each dyslipidemic state: LDL-C in patients with HC, triglycerides and VLDL-C in patients with HTG, or all 3 in patients with CH. Atorvastatin was well-tolerated with a safety profile similar to other drugs in its class

Efficacy of oral ondansetron in the prevention of emesis in outpatients receiving cyclophosphamide-based chemotherapy. The Ondansetron Study Group.

Beck TM, Ciociola AA, Jones SE, et al.

*Ann Intern Med*. 1993 Mar 15; 118(6):407-13.

**OBJECTIVE:** To evaluate the efficacy and safety of oral ondansetron (Zofran) as an antiemetic in patients receiving cyclophosphamide-based chemotherapy. **DESIGN:** A multicenter, randomized, double-blind, stratified, placebo-controlled trial conducted between March 1989 and January 1990. **SETTING:** Twenty-seven oncology centers including university hospitals, community cancer centers, and private medical oncology practices. **PATIENTS:** A total of 349 chemotherapy-naive patients having their first cycle of cyclophosphamide (> or = 450 mg/m<sup>2</sup>)-based chemotherapy. Patients also received methotrexate (> or = 30 mg/m<sup>2</sup>) or doxorubicin (> or = 35 mg/m<sup>2</sup>). All patients were evaluated for safety and 318 (91%) were evaluated for efficacy. **INTERVENTIONS:** Patients were randomly assigned to one of four treatment groups: placebo, 1 mg, 4 mg, or 8 mg of ondansetron. Assigned study medication was taken three times per day for 3 consecutive days. **MEASUREMENTS:** Time and number of emetic episodes as well as degree of nausea were recorded by patients for each of the 3 study days. **RESULTS:** Compared with placebo, all three doses of ondansetron were superior ( $P < 0.001$ ) in preventing vomiting and controlling nausea. A complete response (no emetic episodes) was observed in 19%, 57%, 65%, and 66% of patients in the placebo, 1-mg, 4-mg, and 8-mg ondansetron groups, respectively. For patients who received higher-dose cyclophosphamide and doxorubicin, a dose-related trend in antiemetic efficacy of ondansetron was observed. Mild headache and constipation were the most frequently reported adverse events. No extrapyramidal reactions were observed. **CONCLUSION:** Oral ondansetron is a safe and effective antiemetic that is more efficacious than placebo for patients receiving cyclophosphamide-based chemotherapy

Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial.

Bensen WG, Fiechtner JJ, McMillen JI, et al.

*Mayo Clin Proc*. 1999 Nov; 74(11):1095-105.

**OBJECTIVE:** To compare the efficacy and safety of celecoxib, a cyclooxygenase-2 (COX-2) inhibitor, with those of naproxen, a nonsteroidal anti-inflammatory drug (NSAID), and placebo in the treatment of osteoarthritis of the knee. **METHODS:** In this multicenter, randomized, double-blind, placebo-controlled trial, 1003 patients with symptomatic osteoarthritis of the knee were randomly assigned to receive celecoxib at doses of 50, 100, or 200 mg twice a day; naproxen, 500 mg twice a day; or placebo for 12 weeks. Patients were evaluated with standard measures of efficacy 2 to 7 days after discontinuing previous NSAID or analgesic therapy and after 2, 6, and 12 weeks of treatment with the study drug. **RESULTS:** Celecoxib treatment led to significant improvement in the signs and symptoms of osteoarthritis as determined by all efficacy measures. Significant pain relief occurred within 2 days of the initiation of treatment, and maximum anti-inflammatory and analgesic activity, evident within 2 weeks, was sustained throughout the 12-week study. All celecoxib doses were efficacious compared with placebo, although the 50-mg twice-daily dosage regimen was minimally effective. The higher doses of celecoxib (100 and 200 mg twice a day) were similarly efficacious, and the magnitude of improvement observed with these dosing regimens was comparable to that seen with naproxen at a dose of 500 mg twice a day. All doses of celecoxib and naproxen were well tolerated. **CONCLUSION:** COX-2 inhibition with celecoxib is an effective approach for the treatment of osteoarthritis, as seen by clinical improvement in signs and symptoms comparable to treatment with naproxen

Uneasy alliance--clinical investigators and the pharmaceutical industry.

Bodenheimer T.

*N Engl J Med.* 2000 May 18; 342(20):1539-44.

Oral contraceptives and thromboembolic disease: effects of lowering oestrogen content.

Bottiger LE, Boman G, Eklund G, et al.

*Lancet.* 1980 May 24; 1(8178):1097-101.

The introduction of low-oestrogen oral contraceptives in Sweden and the concomitant disappearance of high-dose preparations did not result in a lowering of the mortality of fertile women from thromboembolic disease. Morbidity due to thromboembolism seems to have fallen, and the number of thromboembolic incidents reported to the Swedish Adverse Drug Reaction Committee decreased dramatically. The decrease was due exclusively to a reduction in venous thromboembolic disease: the frequency of arterial complications (cerebral and coronary) remained constant

51% of U.S. adults take 2 pills or more a day, survey reports.

Bowman L.

*San Diego Union-Tribune.* 2001.Jan.17:A8.

Adverse drug reactions. An overview of special considerations in the management of the elderly patient.

Brawn LA, Castleden CM.

*Drug Saf.* 1990 Nov; 5(6):421-35.

The incidence of adverse drug reactions increases with aging, and the elderly are more likely to suffer serious or fatal reactions. Thus, morbidity and mortality are considerable in old patients, with 15% of those in hospital suffering a reaction, and many admitted as a consequence of one. The greater propensity of older patients for adverse drug reactions largely reflects the prescription of drugs to them, although over-the-counter purchases must also play a part. The elderly take more drugs per se (which is a reflection of multiple pathology), and more drugs with a narrow therapeutic index associated with a high risk of dangerous adverse reactions and drug interactions. They also have a reduced ability to withstand any reactions due to concomitant disease, and an altered pharmacokinetic and -dynamic response which tends to increase drug effects. The recommendation must be to use fewer drugs in older patients, perhaps trying alternative medicine first in nonacute conditions. Starting doses can often be reduced in the elderly, and clinical and therapeutic monitoring of effect is mandatory. The use of diuretics, antihypertensives, anti-Parkinsonian drugs and anticoagulants emphasise these points, and is discussed in detail together with digoxin, analgesics and nonsteroidal anti-inflammatory drugs. Clear guidelines are given for the use of each of these classes of drug

Briefing Book for the Rx to OTC Switch of Pravachol (Pravastatin Sodium).

Bristol-Myers Squibb.

2000.Jul.14

Ibuprofen and aspirin in the treatment of rheumatoid arthritis. A cooperative double-blind trial.

Brooks CD, Schmid FR, Biundo J, et al.

*Rheumatol Phys Med.* 1970; 10:Suppl-63.

Poor response to fluoxetine: underlying depression, serotonergic overstimulation, or a "therapeutic window"?

Cain JW.

*J Clin Psychiatry.* 1992 Aug; 53(8):272-7.

**BACKGROUND:** Symptoms of serotonergic overstimulation may resemble depressive symptoms. Postulating that overmedication with fluoxetine can appear as response failure (as norfluoxetine accumulates), systematic trials of lower doses were conducted in patients who failed to respond despite apparent initial improvements. **METHOD:** Of 23 consecutive outpatients treated with fluoxetine 20 mg/day for DSM-III-R major depression, 4 failed to sustain initial improvements during 4-8 weeks of treatment (in the absence of apparent side effects). In these 4 patients, fluoxetine was withdrawn for 2 weeks, then reinstated at 20 mg q.o.d. All patients were followed up weekly to monthly (for up to 17 months) and administered the 17-item Hamilton Rating Scale for Depression. **RESULTS:** Four of 4 patients improved during washout and went on to respond to the lower dose. All 4 cases are presented. On review of the literature, fluoxetine fixed-dose studies reveal increased adverse effects with no increase in efficacy at dosages above 5 mg/day and decreased efficacy at dosages above 40 mg/day. Special issues inherent in the study and use of an antidepressant with a 1- to 3-week active half-life are discussed. **CONCLUSION:** Even in the apparent absence of side effects, nonresponse to fluoxetine may be due to overmedication in some patients. Standard doses of fluoxetine may be higher than "optimum." The apparent difficulty distinguishing fluoxetine's adverse effects/toxicity (or a "therapeutic window" effect) from underlying depressive symptoms, taken in conjunction with the 3-9 weeks required to approach steady state, may suggest the option of lowering the dose in some cases of nonresponse or "relapse."

Evidence for the cardioprotective effects of omega-3 Fatty acids.

Carroll DN, Roth MT.

*Ann Pharmacother.* 2002 Dec; 36(12):1950-6.

**OBJECTIVE:** To review available literature regarding the cardiovascular effects of marine-derived Omega-3 fatty acids and evaluate the benefit of these fatty acids in the prevention of coronary heart disease. **DATA SOURCES:** Biomedical literature accessed through a MEDLINE search (1966-April 2002). Search terms included fish oil, omega-3 fatty acid, sudden death, hypertriglyceridemia, myocardial infarction, and mortality. **DATA SYNTHESIS:** Following an early 1970's observational investigation that Omega-3 fatty acids may reduce the occurrence of myocardial infarction-related deaths in Greenland Eskimos, additional trials have been conducted that support this finding. Epidemiologic and clinical trial data suggest that Omega-3 fatty acids may reduce the risk of cardiovascular-related death by 29-52%. In addition, the risk of sudden cardiac death was found to be reduced by 45-81%. Possible mechanisms for these beneficial effects include antiarrhythmic properties, improved endothelial function, antiinflammatory action, and reductions in serum triglyceride concentrations. Omega-3 Fatty acids are fairly well tolerated; potential adverse effects include bloating and gastrointestinal distress, "fishy taste" in the mouth, hyperglycemia, increased risk of bleeding, and a slight increase in low-density-lipoprotein cholesterol. **CONCLUSIONS:** Omega-3 Fatty acids may be beneficial and should be considered in patients with documented coronary heart disease. They may be particularly beneficial for patients with risk factors for sudden cardiac death

Clinical experience with Ibuprofen in the treatment of rheumatoid arthritis.

Chalmers TM.

*Ann Rheum Dis.* 1969 Sep; 28(5):513-7.

Influence of age and gender on the plasma profiles of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitory activity following multiple doses of lovastatin and simvastatin.

Cheng H, Rogers JD, Sweany AE, et al.

The effects of age and of gender on the plasma profiles of HMG-CoA reductase inhibitors following separate once-a-day dosage regimens (17 days) of lovastatin (80 mg/day) and simvastatin (40 mg/day) were studied in hypercholesterolemic patients. In general, plasma concentrations of active and total HMG-CoA reductase inhibitors were higher in elderly individuals (age, 70 to 78 years) and in females for both drugs. However, the T<sub>max</sub> of these inhibitors was not significantly affected by either age or gender. Following the last dose of lovastatin, the mean steady-state plasma concentrations of total and active HMG-CoA reductase inhibitors were 30-60% higher in the elderly than in young individuals (age, 19 to 30 years). Also, the mean plasma concentrations were 20-50% higher in female than in male patients. Similarly, following the last dose of simvastatin, the mean plasma concentrations of HMG-CoA reductase inhibitors were 40-60% higher in the elderly than in young patients and were 20-50% higher in female than in male patients. These age- and gender-related differences do not appear to be large enough to warrant modification of dosage regimens, because plasma concentrations of these inhibitors are not necessarily indicative of efficacy and the therapeutic windows for lovastatin and simvastatin are broad

Report on a long-term tolerability study of up to two years with diclofenac sodium (Voltaren).

Ciccolunghi SN, Chaudri HA, Schubiger BI, et al.

*Scand J Rheumatol Suppl.* 1978;(22):86-96.

The value and results of long-term studies with diclofenac sodium (Voltarol).

Ciccolunghi SN, Chaudri HA, Schubiger BI.

*Rheumatol Rehabil.* 1979; Suppl 2:100-15.

The results of 940 patients treated with diclofenac for 3 to 24 months in comparative and non-comparative trials are presented. Maximal improvement tended to occur in the first 3 to 6 months of treatment and was generally maintained. Diclofenac was at least as effective as equivalent doses of indomethacin and naproxen and, when treatment lasts more than 3 months, may be more effective. The majority of patients reporting unwanted effects or discontinuing treatment did so in the first 6 months. Unwanted effects (similar to those in short-term trials) were mainly gastrointestinal. Central nervous system, cardiovascular and dermatological side-effects were reported in 1% or less of patients. The long-term laboratory tolerability of diclofenac was good, with no changes in the nature, frequency or severity of abnormal tests with increasing duration of treatment. During the development of diclofenac sodium (Voltarol) various types of long-term investigation were conducted (Table I). This paper presents the results, covering a total of 940 patients treated for 3-24 months, and discusses their significance

Multiple-dose pharmacokinetics, pharmacodynamics, and safety of atorvastatin, an inhibitor of HMG-CoA reductase, in healthy subjects.

Cilla DD, Jr., Whitfield LR, Gibson DM, et al.

*Clin Pharmacol Ther.* 1996 Dec; 60(6):687-95.

This study examined the pharmacokinetics, pharmacodynamics, and safety of atorvastatin, an investigational inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, in 50 healthy subjects by means of a randomized, double-blind parallel-group design. Volunteers received rising single and multiple doses of 0.5 to 80 mg/day atorvastatin (40 subjects) or placebo (10 subjects). The drug was administered once or twice daily for 14 days. Atorvastatin was well tolerated by healthy subjects. The most common adverse events reported after atorvastatin-headache and nausea-occurred as frequently after placebo. Atorvastatin peak concentration and area under the plasma concentration-time curve (AUC) values increased more than proportionally with atorvastatin dose after both single and multiple drug doses. The extent of atorvastatin absorption (AUC) was similar after once- or twice-daily drug administration. Steady-state drug concentrations were achieved by the third day of drug dosing. Mean elimination half-life values ranged from 11 to 24 hours. Atorvastatin accumulation was approximately 1.5- and 3.0-fold after once- and twice-daily administration, respectively. Atorvastatin produced dose-related reductions in total cholesterol and low-density lipoprotein cholesterol that were similar after once- and twice-daily drug administration. Reductions in mean total cholesterol and low-density lipoprotein cholesterol values ranged from 13% and 22% (2.5 mg/day) to 45% and 58% (80 mg/day), respectively ( $p < \text{or} = \text{"0.0013"}$  in comparison with placebo and with baseline over this dose range). In summary, atorvastatin doses of up to 80 mg/day were well tolerated and had significant cholesterol-lowering effects

Scientists study gender gap in drug responses.

Cimons M.

*Los Angeles Times*. 1999.Jun.6(A1):89.

Goth's Medical Pharmacology, 1992.

Clark WGBDCJAR.

1992; Thirteenth Edition

Goth's Medical Pharmacology.

Clark WGBDCJAR.

1992; Thirteenth Edition

Healing and recurrence of active duodenal ulcer with nizatidine.

Cloud ML, Offen WW, Matsumoto C, et al.

*Clin Pharmacol Ther*. 1989 Sep; 46(3):310-6.

Nizatidine, a new H<sub>2</sub>-receptor antagonist for treatment of duodenal ulcer disease, was evaluated in a unique two-phase, placebo-controlled, randomized, double-blind, multicenter clinical trial. Patients received either 150 mg nizatidine twice daily or placebo for 4 weeks (phase I). If ulcer healing did not occur during phase I, patients were randomly reallocated to receive either 150 mg nizatidine twice daily or placebo for an additional 4 weeks (phase II). Patients with a healed ulcer continued on the same therapy. All patients were endoscoped at week 8. Healing rates at week 2 were 93 of 265 (35%) nizatidine-treated patients and 55 of 260 (21%) placebo-treated patients ( $p$  less than 0.001); at week 4, healing rates were 198 of 259 (76%) nizatidine-treated patients and 95 of 243 (39%) placebo-treated patients ( $p$  less than 0.001). In phase II, ulcer healing occurred in 46 of 86 (53%) nizatidine-treated patients and in 23 of 90 (26%) placebo-treated patients ( $p = 0.002$ ). In patients who had a healed ulcer at previous endoscopies, 18 of 178 (10%) nizatidine-treated patients and 10 of 81 (12%) placebo-treated patients had a recurrence of duodenal ulcer. Smokers who had histories of previous ulcers were more likely to have an early recurrence

The one-size dose does not fit all: look beyond the guidelines of drug manufacturers.

Cohen JS.

*Newsweek*. 1999.Dec.6:92.

Should patients be given an initial low test dose of sildenafil?

Cohen JS.

*Drug Saf*. 2000 Jul; 23(1):1-9.

Sildenafil is highly effective for treating erectile dysfunction (ED). However, its use has been associated with serious adverse events including myocardial infarctions and strokes, and 130 verifiable plus 112 unverified deaths reported to the US Food and Drug Administration during the 8 months after sildenafil was introduced in the US, and 522 reported deaths during the 13.5 months after its introduction. Moreover, some events have occurred in men taking their first dose of the agent, suggesting that sildenafil, like some drugs that affect blood pressure, may provoke a first-dose reaction. This possibility warrants extra caution to be used when initiating treatment with sildenafil. Such caution is not currently provided by the current dosage guidelines that, for example, recommend the use of sildenafil 50 mg initially for most men between the ages of 18 and 65 years, despite wide differences in bodyweight, age, drug metabolism, health status and usage of other medications. It can be difficult to identify the patient who may be unusually sensitive to the effects of sildenafil. Exercise stress tests have been recommended, but serious adverse events have occurred in men with normal stress tests following the ingestion of sildenafil. Blood pressure monitoring following sildenafil administration will not prevent a serious adverse drug event already in progress. This article discusses the advantages and disadvantages of initiating treatment with a low test dose of sildenafil, performed at home or in the doctor's office. The advantages of this approach include: (i) identifying patients who are highly sensitive to the effects of sildenafil and who may need no higher dose; (ii) minimising adverse effects such as flushing and dizziness that often frighten patients and may affect adherence; (iii) avoidance of major adverse events; and (iv) reassuring patients with ED who remain wary about trying sildenafil therapy

Adverse drug effects, compliance, and initial doses of antihypertensive drugs recommended by the Joint National Committee vs the Physicians' Desk Reference.

Cohen JS.

*Arch Intern Med.* 2001 Mar 26; 161(6):880-5.

**BACKGROUND:** Compliance problems are common causes of the inadequate treatment of hypertension, with 16% to 50% of patients quitting treatment within 1 year. Dose-related adverse drug events (ADEs) frequently cause compliance problems, and many ADEs occur with the initial doses of antihypertensive drugs. Thus, it is an established tenet to initiate antihypertensive therapy at low doses to avoid ADEs that diminish patients' quality of life and reduce compliance. However, what are the lowest effective doses of antihypertensive drugs? **OBJECTIVE:** To compare the initial doses recommended in the Physicians' Desk Reference (PDR) with those recommended by the Sixth Report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). **METHODS:** Review of the latest JNC VI report (1997) and the 1999 and 2000 editions of the PDR and the medical literature. **RESULTS:** The JNC VI recommends substantially lower initial doses for 23 (58%) of 40 drugs, compared with the PDR. In addition, for 37 (82%) of 45 drugs, PDR guidelines do not suggest lower initial doses for old or frail patients than for younger adults. **CONCLUSIONS:** Although the PDR is the drug reference most used by physicians, it does not reflect the lowest initial doses that are recommended by the JNC VI for many of the most prescribed antihypertensive drugs. Because avoidance of ADEs is essential to maintaining compliance with antihypertensive therapy, and because many antihypertensive ADEs are dose related, physicians must know the very lowest, effective, least ADE-prone doses. Patients and physicians would benefit by establishing mechanisms to make this information readily available to all practicing physicians

Reduction of aspirin-induced fecal blood loss with low-dose misoprostol tablets in man.

Cohen MM, Clark L, Armstrong L, et al.

*Dig Dis Sci.* 1985 Jul; 30(7):605-11.

Misoprostol (SC-29333), a synthetic prostaglandin E1 methyl ester analog, was given simultaneously with acetylsalicylic acid in a double-blind, placebo-controlled randomized prospective study of 32 healthy human male subjects. Fecal blood loss was measured for eight days using the <sup>51</sup>Cr-labeled red blood cell technique. Aspirin (650 mg qid) and misoprostol (25 micrograms qid) or placebo were given during days 3, 4, and 5. There was a significant (P less than 0.05) increase in median blood loss (modified Friedman test) from 0.81 to 6.05 ml/day in the aspirin with placebo group (N = 16). Median blood loss was increased (from 0.75 to 3.75 ml/day) in the aspirin with misoprostol group (N = 16), but this was significantly less (Mann-Whitney U test, P less than 0.01) than the placebo group. Mean serum salicylate concentrations in the placebo and misoprostol groups were similar (7.8 and 6.8 micrograms/ml, respectively). There were no significant changes in laboratory values in any of the subjects studied, nor were any major side-effects encountered. This study demonstrates that oral misoprostol reduces aspirin-induced gastrointestinal bleeding even when administered simultaneously and at a dose level below its threshold for significant acid inhibition. This indicates a potential role for misoprostol in the prevention of gastric mucosal damage in selected patients

Exploring the Biological Contributions to Human Health: Does Sex Matter? 2001. .: .

Committee on Understanding the Biology of Sex and Gender Differences BoHSP, Institute of Medicine NAOs.

2004

Sponsorship, authorship, and accountability.

Davidoff F, DeAngelis CD, Drazen JM, et al.

*N Engl J Med.* 2001 Sep 13; 345(11):825-6.

Efficacy on climacteric symptoms and safety of low dose estradiol transdermal matrix patches. A randomized, double-blind placebo-controlled study.

de Aloysio D, Rovati LC, Giacovelli G, et al.

*Arzneimittelforschung.* 2000 Mar; 50(3):293-300.

Two estradiol (E2) transdermal patches releasing 25 micrograms/day E2 (D-25) or 37.5 micrograms/day E2 (D-37.5) were compared to a placebo patch on 156 patients in natural or surgical menopause suffering from at least 5 hot flushes per day,

randomly and blindly assigned to three parallel groups of 52 patients each, to be treated continuously for 12 weeks, without progestin opposition. "Responders" (patients with less than 3 hot flushes per day at the end of treatment), were 82% and 90% under D-25 or D-37.5, respectively, both significantly ( $p < 0.001$ ) more than under placebo (44%). Comparable efficacy was observed on severity of hot flushes, Kupperman Index and on the self-rated efficacy. Systemic adverse events occurred in 10%, 10% and 8% of patients, respectively, under D-25, D-37.5 or placebo. Occasional mild and transient itching and/or erythema on the site of application was reported by few patients and did never require discontinuation of application. In conclusion D-25 and D-37.5 were significantly more effective than placebo in relieving climacteric symptoms and were systemically and locally as well tolerated as placebo. D-25 (Demestril 25) releasing 25 micrograms/day E2 can therefore be recommended for low-dosed estrogen replacement therapy

Placebo controlled studies with ranitidine in duodenal ulcer.

Dobrilla G, Barbara L, Bianchi PG, et al.

*Scand J Gastroenterol Suppl.* 1981 Jun; 69:101-7.

171 duodenal ulcer patients were treated for four weeks with either ranitidine or placebo under double-blind conditions. 40 patients (monocentre study) received ranitidine (40 mg), or placebo t.d.s. with meals and 80 mg at bedtime. 131 patients (multicentre study) received ranitidine (150 mg), or placebo b.d. In the monocentre study endoscopy after 4 weeks of treatment showed complete healing in 83.3% of the ranitidine patients and 30.4% of those on placebo ( $P$  less than 0.01%). In the multicentre study the healing percentages were 79.4% and 30.4%, respectively ( $P$  less than 0.001). In both trials pain and antacid consumption decreased in patients taking ranitidine more than in patients on placebo. After 4 weeks in the double blind studies 13 of the 15 patients with unhealed ulcer in the monocentre study and 51 of 54 patients in the multicentre study received open treatment with ranitidine for another 4 week period. The overall healing percentages by the 8th week of treatment with ranitidine were 94.4% and 93.6% respectively. No serious side effects, or haematological changes were observed during the treatment with ranitidine

Hypertension in patients with diabetes. Overcoming barriers to effective control.

Elliott WJ, Maddy R, Toto R, et al.

*Postgrad Med.* 2000 Mar; 107(3):29-6, 38.

The management of diabetic hypertension poses special problems for the medical community. Although patient adherence is often a major barrier to successful management, physicians' beliefs and prejudices also negatively impact treatment. In addition, healthcare organizations need to provide better support to physicians who feel isolated in their efforts to manage diabetic hypertension. Reductions of morbidity and mortality are achievable goals but require aggressive treatment and improved adherence if they are to be reached

Personal perspective on low-dosage estrogen therapy for postmenopausal women.

Ettinger B.

*Menopause.* 1999; 6(3):273-6.

OBJECTIVE: As evidenced by results from recent clinical trials and epidemiological studies that have examined the physiological and clinical effects of low levels of estradiol, it is now time to replace the widely held belief that less than the standard dosage of estrogen is without benefit. DESIGN: Review of literature and personal experience. RESULTS: Studies indicate that low-dosage estrogen can relieve vasomotor symptoms, can prevent bone loss, and may reduce the risk of coronary heart disease. However, to achieve these health benefits, long-term estrogen use is required. Women who use low dosages of estrogens are less likely to have unacceptable side effects, such as irregular bleeding, heavy bleeding, or breast tenderness. Thus, long-term continuance of hormone replacement therapy (HRT) may be improved if lower dosages are given, particularly if the HRT regimen is tailored to the needs of the patient. CONCLUSIONS: Although standard-dosage estrogen remains the "gold standard" for HRT, having a low dosage as an alternative regimen can be useful. Attention of clinical researchers should focus on the effects of low-dosage estrogen on osteoporotic fractures and other health outcomes

Personal perspective on low-dosage estrogen therapy for postmenopausal women.

Ettinger B.

*Menopause.* 1999; 6(3):273-6.

**OBJECTIVE:** As evidenced by results from recent clinical trials and epidemiological studies that have examined the physiological and clinical effects of low levels of estradiol, it is now time to replace the widely held belief that less than the standard dosage of estrogen is without benefit. **DESIGN:** Review of literature and personal experience. **RESULTS:** Studies indicate that low-dosage estrogen can relieve vasomotor symptoms, can prevent bone loss, and may reduce the risk of coronary heart disease. However, to achieve these health benefits, long-term estrogen use is required. Women who use low dosages of estrogens are less likely to have unacceptable side effects, such as irregular bleeding, heavy bleeding, or breast tenderness. Thus, long-term continuance of hormone replacement therapy (HRT) may be improved if lower dosages are given, particularly if the HRT regimen is tailored to the needs of the patient. **CONCLUSIONS:** Although standard-dosage estrogen remains the "gold standard" for HRT, having a low dosage as an alternative regimen can be useful. Attention of clinical researchers should focus on the effects of low-dosage estrogen on osteoporotic fractures and other health outcomes

Drug prescribing for the elderly.

Everitt DE, Avorn J.

*Arch Intern Med.* 1986 Dec; 146(12):2393-6.

Mevacor OTC. 2000 Jun. Rockville, MD.

FDA.

2004

Subacute hepatic failure associated with a new antidiabetic agent, troglitazone: a case report with autopsy examination.

Fukano M, Amano S, Sato J, et al.

*Hum Pathol.* 2000 Feb; 31(2):250-3.

An autopsy case of fatal subacute hepatic failure after administration of troglitazone is described. The liver dysfunction developed about five months after the patient, a sixty-three-year-old woman, had been initially treated with troglitazone. The patient developed hepatic failure and died despite various hepatic auxiliary treatments such as plasmapheresis. Autopsy findings revealed focal liver cell necrosis, cholestasis and steatosis with infiltration of lymphocytes and neutrophils and lack of regenerative activity. The causative mechanism of liver dysfunction may be metabolite aberration, as a result of accumulation of hepatotoxic metabolite(s), in a category of idiosyncratic liver injury. It is proposed to monitor liver function strictly and periodically for the diabetic patients prescribed troglitazone

Statins and risk of polyneuropathy: a case-control study.

Gaist D, Jeppesen U, Andersen M, et al.

*Neurology.* 2002 May 14; 58(9):1333-7.

**BACKGROUND:** Several case reports and a single epidemiologic study indicate that use of statins occasionally may have a deleterious effect on the peripheral nervous system. The authors therefore performed a population-based study to estimate the relative risk of idiopathic polyneuropathy in users of statins. **METHOD:** The authors used a population-based patient registry to identify first-time-ever cases of idiopathic polyneuropathy registered in the 5-year period 1994 to 1998. For each case, validated according to predefined criteria, 25 control subjects were randomly selected among subjects from the background population matched for age, sex, and calendar time. The authors used a prescription register to assess exposure to drugs and estimated the odds ratio of use of statins (ever and current use) in cases of idiopathic polyneuropathy compared with control subjects. **RESULTS:** The authors verified a diagnosis of idiopathic polyneuropathy in 166 cases. The cases were classified as definite (35), probable (54), or possible (77). The odds ratio linking idiopathic polyneuropathy with statin use was 3.7 (95% CI 1.8 to 7.6) for all cases and 14.2 (5.3 to 38.0) for definite cases. The corresponding odds ratios in current users were 4.6 (2.1 to 10.0) for all cases and 16.1 (5.7 to 45.4) for definite cases. For patients treated with statins for 2 or more years the odds ratio of definite idiopathic polyneuropathy was 26.4 (7.8 to 45.4). **CONCLUSIONS:** Long-term exposure to statins may substantially increase the risk of polyneuropathy

Women Sufficiently Represented in New Drug Testing, but FDA Oversight Needs Improvement.

GAO.

Rational drug therapy in the elderly or how not to poison your elderly patients.

Gibian T.

*Aust Fam Physician*. 1992 Dec; 21(12):1755-60.

Adverse drug reactions are more common and more serious in the elderly. Illness caused by medications is arguably the most significant treatable geriatric health problem. In this review, the author discusses the scope and origins of the problems, and describes some principles for minimising drug toxicity

Goodman and Gilman's: The Pharmacological Basis of Therapeutics .

Gilman AGRTWNASTP.

1996;

Dietary supplementation with omega-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico.

GISSI-Prevenzione Investigators.

*Lancet*. 1999; 354(44755)

Too much of a good thing? Doctor challenges drug manual.

Grady D.

*New York Times*. 1999.Oct.12:D12.

Fluoxetine.

Gram LF.

*N Engl J Med*. 1994; 331(135461)

Symptom relief and side effects of postmenopausal hormones: results from the Postmenopausal Estrogen/Progestin Interventions Trial.

Greendale GA, Reboussin BA, Hogan P, et al.

*Obstet Gynecol*. 1998 Dec; 92(6):982-8.

**OBJECTIVE:** To assess pair-wise differences between placebo, estrogen, and each of three estrogen-progestin regimens on selected symptoms. **METHODS:** This was a 3-year, multicenter, double-blind, placebo-controlled trial in 875 postmenopausal women aged 45-64 years at baseline. Participants were assigned randomly to one of five groups: 1) placebo, 2) daily conjugated equine estrogens, 3) conjugated equine estrogens plus cyclical medroxyprogesterone acetate, 4) conjugated equine estrogens plus daily medroxyprogesterone acetate, and 5) conjugated equine estrogens plus cyclical micronized progesterone. Symptoms were self-reported using a checklist at 1 and 3 years. Factor analysis reduced 52 symptoms to a set of six symptom groups. **RESULTS:** In intention-to-treat analyses at 1 year, each active treatment demonstrated a marked, statistically significant, protective effect against vasomotor symptoms compared with placebo (odds ratios [ORs] 0.17-0.28); there was no additional benefit of estrogen-progestin over estrogen alone. Only progestin-containing regimens were significantly associated with higher levels of breast discomfort (OR 1.92-2.27). Compared with placebo, women randomized to conjugated equine estrogens reported no increase in perceived weight. Those randomized to medroxyprogesterone acetate reported less perceived weight gain (OR 0.61-0.69) than placebo. Anxiety, cognitive, and affective symptoms did not differ by treatment assignment. Analyses restricted to adherent women were not materially different than those using intention-to-treat, except that women adherent to medroxyprogesterone acetate and micronized progesterone regimens reported fewer musculoskeletal symptoms (OR 0.62-0.68). **CONCLUSION:** These results confirm the usefulness of post-menopausal hormone therapy for hot flashes, show

convincingly that estrogen plus progestin causes breast discomfort, and demonstrate little influence of postmenopausal hormones on anxiety, cognition, or affect

Symptom relief and side effects of postmenopausal hormones: results from the Postmenopausal Estrogen/Progestin Interventions Trial.

Greendale GARBAHPBVMSSJSB-CE.

*Obstet Gynecol.* 1998; 92(9828.6)

Claritin and Schering-Plough: a prescription for profit.

Hall SS.

*New York Times.* 2001.Mar.11

When doctors go to class, industry often foots the bill.

Hensley S.

*Wall Street Journal.* 2002.Dec.4: A1.

How much drug in the tablet?

Herxheimer A.

*Lancet.* 1991 Feb 9; 337(8737):346-8.

Many recommended drug doses are higher than necessary, for two reasons. Drugs are often introduced at a dose that will be effective in around 90% of the target population, because this helps market penetration. Doses are also partly determined by an irrational preference for round numbers. The dose excess due to such digit preference may be as much as 70% of the correct dose and on average is probably 25%. Needlessly high doses are bound to cause avoidable unwanted effects in a proportion of patients. Rigorous methods must be used to determine the doses recommended and the amount of drug to be put into a tablet or other dosage form

How much drug in the tablet?1991.

Herxheimer A.

*Lancet.* 2004 Feb 9; 337(8737):346-8.

Double-blind crossover trial comparing ibuprofen with flufenamic acid in rheumatoid arthritis.

Hingorani K.

*Rheumatol Phys Med.* 1970; 10:Suppl-82.

Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis.

Holt S, Suder A, Weatherall M, et al.

*BMJ.* 2001 Aug 4; 323(7307):253-6.

OBJECTIVE: To examine the dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma. DESIGN: Meta-analysis of placebo controlled, randomised clinical trials that presented data on at least one outcome measure of asthma and that used at least two different doses of fluticasone. SETTING: Medline, Embase, and GlaxoWellcome's internal clinical study registers. MAIN OUTCOME MEASURES: FEV(1), morning and evening peak expiratory flow, night awakenings, beta agonist use, and major exacerbations. RESULTS: Eight studies, with 2324 adolescents and adults with asthma, met the inclusion criteria. Data on doses of >500 microg/day were limited. The dose-response curve for the raw data began to reach a plateau at around 100-200 microg/day and peaked by 500 microg/day. A negative exponential model for the data, without meta-

analysis, indicated that 80% of the benefit at 1000 microg/day was achieved at doses of 70-170 microg/day and 90% by 100-250 microg/day. A quadratic meta-regression showed that the maximum achievable efficacy was obtained by doses of around 500 microg/day. The odds ratio for patients remaining in a study at a dose of 200 microg/day, compared with higher doses, was 0.73 (95% confidence interval 0.49 to 1.08). Comparison of the standardised difference in FEV(1) for an inhaled dose of 200 microg/day against higher doses showed a difference in FEV(1) of 0.13 of a standard deviation (-0.02 to 0.29). CONCLUSIONS: In adolescent and adult patients with asthma, most of the therapeutic benefit of inhaled fluticasone is achieved with a total daily dose of 100-250 microg, and the maximum effect is achieved with a dose of around 500 microg/day. However, these findings were limited by the lack of data on individual patients and by the paucity of dose-response studies that included doses of >500 microg/day

Commentary: Dosage needs systematic and critical review; Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis. 2001 Aug 4; .

Holt SSAWMCSSPBR.

*Br Med J.* 2001 Aug 4; 323:253.-256.

Herxheimer, A. (Emeritus Fellow, Cochrane Centre, London)

Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology.

Israili ZH, Hall WD.

*Ann Intern Med.* 1992 Aug 1; 117(3):234-42.

OBJECTIVE: To review available information on cough and angioneurotic edema associated with angiotensin-converting enzyme (ACE) inhibitors. DATA SOURCES: All relevant articles from 1966 through 1991 were identified mainly through MEDLINE search and article bibliographies. STUDY SELECTION: More than 400 articles were identified; 200 reporting incidence or possible mechanisms for the side effects or both were selected. DATA EXTRACTION AND SYNTHESIS: All pertinent information, including incidence and mechanisms of ACE inhibitor-induced cough and angioedema, was reviewed and collated. CONCLUSIONS: Cough occurs in 5% to 20% of patients treated with ACE inhibitors, recurring with reintroduction of the same or another ACE inhibitor. It is more common in women. The mechanism may involve accumulation of prostaglandins, kinins (such as bradykinin), or substance P (neurotransmitter present in respiratory tract C-fibers); both bradykinin and substance P are degraded by ACE. A 4-day trial of withdrawal of the ACE inhibitor or temporary substitution of another class of antihypertensive agent inexpensively and easily ascertains if the ACE inhibitor caused the cough. Change to another ACE inhibitor or additive therapy with nonsteroidal anti-inflammatory drugs is not recommended. Prompt recognition of ACE inhibitor-related cough can prevent unnecessary diagnostic testing and treatment. Angioedema occurs in 0.1% to 0.2% of patients receiving ACE inhibitors. The onset usually occurs within hours or, at most, 1 week after starting therapy. The mechanism may involve autoantibodies, bradykinin, or complement-system components. Treatment involves first protecting the airway, followed by epinephrine, antihistamines, and corticosteroids if needed. Therapy is then resumed with an alternate class of antihypertensive agent

Private practice evaluation of the safety and efficacy of bupropion in depressed outpatients.

Kirksey DF, Harto-Truax N.

*J Clin Psychiatry.* 1983 May; 44(5 Pt 2):143-7.

A multicenter uncontrolled 4-week trial of bupropion in depressed outpatients was conducted in the private practices of 25 internists, 9 family practitioners, and 3 psychiatrists. Minimum exclusion criteria were used with respect to concurrent medical ailments, age, and concomitant medications. Of the 380 patients admitted to the study, 325 were included in efficacy analyses, and 359 provided data for safety analyses. The average patient was a 51-year-old married white woman with a high school education and a skilled job. Bupropion administered in doses of 150-450 mg/day was highly effective in reducing depressive symptomatology as evaluated by the Hamilton Depression and Clinical Global Impressions scales, and the Zung Self-Rating Scale. No clinically significant bupropion-related changes in blood pressure, pulse rates, respiration rate, body temperature, or laboratory parameters were recorded; only 41 patients were discontinued due to intolerance to adverse experiences. There was a notable absence of daytime sedation, and of anticholinergic and cardiovascular side effects

Mars and Venus and drugs: sex differences create extra risks for women.

Kritz FL.

*Washington Post*. 2001.Feb.20:17.

Menopausal hormone replacement therapy and risk of ovarian cancer.

Lacey JV, Jr., Mink PJ, Lubin JH, et al.

*JAMA*. 2002 Jul 17; 288(3):334-41.

CONTEXT: The association between menopausal hormone replacement therapy and ovarian cancer is unclear. OBJECTIVE: To determine whether hormone replacement therapy using estrogen only, estrogen-progestin only, or both estrogen only and estrogen-progestin increases ovarian cancer risk. DESIGN: A 1979-1998 cohort study of former participants in the Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program. SETTING: Twenty-nine US clinical centers. PARTICIPANTS: A total of 44 241 postmenopausal women (mean age at start of follow-up, 56.6 years). MAIN OUTCOME MEASURE: Incident ovarian cancer. RESULTS: We identified 329 women who developed ovarian cancer during follow-up. In time-dependent analyses adjusted for age, menopause type, and oral contraceptive use, ever use of estrogen only was significantly associated with ovarian cancer (rate ratio [RR], 1.6; 95% confidence interval [CI], 1.2-2.0). Increasing duration of estrogen-only use was significantly associated with ovarian cancer: RRs for 10 to 19 years and 20 or more years were 1.8 (95% CI, 1.1-3.0) and 3.2 (95% CI, 1.7-5.7), respectively (P value for trend <.001), and we observed a 7% (95% CI, 2%-13%) increase in RR per year of use. We observed significantly elevated RRs with increasing duration of estrogen-only use across all strata of other ovarian cancer risk factors, including women with hysterectomy. The RR for estrogen-progestin use after prior estrogen-only use was 1.5 (95% CI, 0.91-2.4), but the RR for estrogen-progestin-only use was 1.1 (95% CI, 0.64-1.7). The RRs for less than 2 years and 2 or more years of estrogen-progestin-only use were 1.6 (95% CI, 0.78-3.3) and 0.80 (95% CI, 0.35-1.8), respectively, and there was no evidence of a duration response (P value for trend = ".30)." CONCLUSION: Women who used estrogen-only replacement therapy, particularly for 10 or more years, were at significantly increased risk of ovarian cancer in this study. Women who used short-term estrogen-progestin-only replacement therapy were not at increased risk, but risk associated with short-term and longer-term estrogen-progestin replacement therapy warrants further investigation

Timing of new black box warnings and withdrawals for prescription medications.

Lasser KE, Allen PD, Woolhandler SJ, et al.

*JAMA*. 2002 May 1; 287(17):2215-20.

CONTEXT: Recently approved drugs may be more likely to have unrecognized adverse drug reactions (ADRs) than established drugs, but no recent studies have examined how frequently postmarketing surveillance identifies important ADRs. OBJECTIVE: To determine the frequency and timing of discovery of new ADRs described in black box warnings or necessitating withdrawal of the drug from the market. DESIGN AND SETTING: Examination of the Physicians' Desk Reference for all new chemical entities approved by the US Food and Drug Administration between 1975 and 1999, and all drugs withdrawn from the market between 1975 and 2000 (with or without a prior black box warning). MAIN OUTCOME MEASURES: Frequency of and time to a new black box warning or drug withdrawal. RESULTS: A total of 548 new chemical entities were approved in 1975-1999; 56 (10.2%) acquired a new black box warning or were withdrawn. Forty-five drugs (8.2%) acquired 1 or more black box warnings and 16 (2.9%) were withdrawn from the market. In Kaplan-Meier analyses, the estimated probability of acquiring a new black box warning or being withdrawn from the market over 25 years was 20%. Eighty-one major changes to drug labeling in the Physicians' Desk Reference occurred including the addition of 1 or more black box warnings per drug, or drug withdrawal. In Kaplan-Meier analyses, half of these changes occurred within 7 years of drug introduction; half of the withdrawals occurred within 2 years. CONCLUSIONS: Serious ADRs commonly emerge after Food and Drug Administration approval. The safety of new agents cannot be known with certainty until a drug has been on the market for many years

Omeprazole 20 mg three days a week and 10 mg daily in prevention of duodenal ulcer relapse. Double-blind comparative trial.

Lauritsen K, Andersen BN, Laursen LS, et al.

*Gastroenterology*. 1991 Mar; 100(3):663-9.

In a double-blind, parallel-group clinical trial of 195 patients with duodenal ulcers who after a short-term study had relief of pain and healed ulcers proved endoscopically, 65 were randomized to receive 20 mg omeprazole 3 days a week (once in the morning from Friday to Sunday), 64 to receive 10 mg omeprazole once daily in the morning, and 66 to receive placebo for up to 6 months. The patients underwent repeat endoscopy with biopsy of the gastric fundic mucosa (qualitative assessment of argyrophilic cell population), assessment of symptoms, and laboratory screening with measurement of basal serum gastrin concentrations at 3 and 6 months or more often if indicated by recurrence of symptoms. At 3 months, endoscopically proved ulcer relapse occurred in 16% receiving 20 mg omeprazole 3 days a week; 21% receiving 10 mg omeprazole daily; and 50%

receiving placebo. At 6 months, corresponding rates were 23%, 27%, and 67% with 95% confidence intervals of difference between the placebo group and omeprazole groups of 28%-60% and 24%-56% (P less than 0.00001), respectively, and between omeprazole groups of -19%-11% (NS). No major clinical or laboratory side effects were noted. Thus both omeprazole regimens are effective and safe in preventing duodenal ulcer relapse

Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies.

Lazarou J, Pomeranz BH, Corey PN.

*JAMA*. 1998 Apr 15; 279(15):1200-5.

**OBJECTIVE:** To estimate the incidence of serious and fatal adverse drug reactions (ADR) in hospital patients. **DATA SOURCES:** Four electronic databases were searched from 1966 to 1996. **STUDY SELECTION:** Of 153, we selected 39 prospective studies from US hospitals. **DATA EXTRACTION:** Data extracted independently by 2 investigators were analyzed by a random-effects model. To obtain the overall incidence of ADRs in hospitalized patients, we combined the incidence of ADRs occurring while in the hospital plus the incidence of ADRs causing admission to hospital. We excluded errors in drug administration, noncompliance, overdose, drug abuse, therapeutic failures, and possible ADRs. Serious ADRs were defined as those that required hospitalization, were permanently disabling, or resulted in death. **DATA SYNTHESIS:** The overall incidence of serious ADRs was 6.7% (95% confidence interval [CI], 5.2%-8.2%) and of fatal ADRs was 0.32% (95% CI, 0.23%-0.41%) of hospitalized patients. We estimated that in 1994 overall 2216000 (1721000-2711000) hospitalized patients had serious ADRs and 106000 (76000-137000) had fatal ADRs, making these reactions between the fourth and sixth leading cause of death. **CONCLUSIONS:** The incidence of serious and fatal ADRs in US hospitals was found to be extremely high. While our results must be viewed with circumspection because of heterogeneity among studies and small biases in the samples, these data nevertheless suggest that ADRs represent an important clinical issue

Gender-related response to fluvastatin in patients with heterozygous familial hypercholesterolaemia.

Leitersdorf E.

*Drugs*. 1994; 47 Suppl 2:54-8.

Hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors are potent cholesterol reducing agents that have been successfully used for the treatment of heterozygous familial hypercholesterolaemia (FH). A recent investigation revealed that several constitutional and genetic factors significantly determined the response of plasma lipids and lipoproteins to the HMG CoA reductase inhibitor fluvastatin. Gender has been identified through multivariate analysis as a major determinant of the plasma high density lipoprotein (HDL) cholesterol response. The current analysis was undertaken to determine possible gender-related fluvastatin dose-response differences. The analysis revealed that for HDL cholesterol, gender-related differences reach statistical significance only at the highest fluvastatin dose of 40 mg/day (females 22.9%, males 12.9%,  $p < 0.01$ ). In parallel, the change in low density lipoprotein (LDL) cholesterol: HDL cholesterol ratio, an indicator of ischaemic heart disease risk, was also found to be affected by gender (females -38.4%, males -32.2%,  $p < 0.01$ ). For LDL cholesterol, no consistent gender-related differences were found. In conclusion, the response of plasma lipid levels to fluvastatin in heterozygote FH patients is significantly affected by gender, with females achieving a more marked overall response, as indicated by higher HDL cholesterol levels and a lower LDL cholesterol: HDL cholesterol ratio

Characteristics and treatment of hypertension in women: a review of the literature.

Lewis CE.

*Am J Med Sci*. 1996 Apr; 311(4):193-9.

Although there are documented differences between women and men in frequency and severity of hypertension and in the relation between hypertension and cardiovascular risk, few studies have been designed to evaluate efficacy and safety of antihypertensive therapy in women. Efficacy of nonpharmacologic interventions to lower blood pressure may differ between the sexes; women have greater difficulty losing weight than men but may respond better than men to dietary sodium reduction. In general, women and men do not respond differently to antihypertensive therapy; however, there may be differences in response to certain classes of antihypertensives. There are limited data on safety of specific antihypertensive agents in women. In some studies, researchers found a greater incidence of adverse effects in women. Effects on sexual functioning and pharmacokinetic and pharmacodynamic characteristics of antihypertensive drugs in women have been studied inadequately. More data are needed to guide the management of hypertension in women

Use of low-dose fluoxetine in major depression and panic disorder.

Louie AK, Lewis TB, Lannon RA.

*J Clin Psychiatry.* 1993 Nov; 54(11):435-8.

**BACKGROUND:** Recent reports suggest that fluoxetine in doses less than the standard 20 mg/day may be effective in the treatment of depression and that some patients, particularly those with panic disorder, may be intolerant of the 20 mg/day dose. We examined the utility of starting fluoxetine at a low daily dose (5 mg) and increasing to the standard daily dose (20 mg) in depressed outpatients with and without concurrent panic disorder. **METHOD:** One hundred thirty-three consecutive outpatients meeting DSM-III-R criteria for major depression were studied. Patients were started on fluoxetine 5 mg/day and were gradually increased to 20 mg/day over a 1-week period. Patients who were unable to reach the 20 mg/day dose were instructed to take the highest tolerable dose for the duration of the study. After a month of fluoxetine treatment, patients were evaluated for compliance with treatment and improvement on the Clinical Global Improvement scale. **RESULTS:** Twenty-eight percent of the patients were unable to increase the dose to the full 20 mg. Of these patients, half could not tolerate doses lower than 20 mg and discontinued the drug, while the other half did well clinically on the lower doses. Patients who discontinued fluoxetine tended to have panic disorder in addition to depression. **CONCLUSION:** We conclude that starting fluoxetine at doses lower than 20 mg is a useful strategy because of the substantial fraction of patients who cannot tolerate a 20-mg dose but appear to benefit from lower doses. This dosing strategy may be of particular benefit for patients with panic disorder

The rise and fall of the killer drug Rezulin.

Lundblad JKS.

*LA Times.* 2000

"Not just a statistic": the history of USA and UK policy over thrombotic disease and the oral contraceptive pill, 1960s-1970s.

Marks L.

*Soc Sci Med.* 1999 Nov; 49(9):1139-55.

Today it is estimated that over 100 million women worldwide have taken the oral contraceptive pill since 1956, when the first clinical trials were undertaken. Since its introduction on to the American market in 1960 and the British one in 1961, the pill has become one of the most popular contraceptives in both countries. Unlike other forms of drugs, which have primarily been formulated to prevent or cure illness, the oral contraceptive pill was designed to be given to healthy women over long periods of time, making the necessity for regulation and medical monitoring that much more pertinent. Focusing on the USA and Britain, this paper concentrates on the different ways in which each country has monitored and secured the safety of the pill between 1960 and 1970. While the British government decided to phase-out high dose oestrogen contraceptive pills associated with thrombotic disease in 1969, such pills continued to be available in the USA through to the 1980s, with measures instead being directed towards supplying better information to patients about the possible side-effects of the pill. The paper explores the reasons for this difference in policy, showing how it was shaped by the particular research orientation of each country as well as the specific legal, medical, social and political traditions within Britain and the USA

Hazards of Medication: A Manual on Drug Interactions, Contraindications, and Adverse Reactions with Other Prescribing and Drug Information.

Martin EW.

1978; Second Edition

Is alternate daily dose of atorvastatin effective in treating patients with hyperlipidemia? The Alternate Day Versus Daily Dosing of Atorvastatin Study (ADDAS).

Matalka MS, Ravnan MC, Deedwania PC.

*Am Heart J.* 2002 Oct; 144(4):674-7.

**BACKGROUND:** The objective of this pilot study was to evaluate the comparative efficacy of alternate-day dosing of atorvastatin compared with the standard once-daily dose based on mean low-density lipoprotein (LDL) reduction from baseline at 6 and 12 weeks of treatment. **METHODS:** In a double-blind, placebo-controlled design, 35 eligible patients who met the National Cholesterol Education Program (NCEP) Adult Treatment Panel II (ATP II) guidelines for drug therapy, depending on their risk

factors, were randomly assigned to receive 10 mg of atorvastatin as an initial dose every day or every other day. Patients were assessed at 6 and 12 weeks as to whether they met the LDL-C goal, and the dose was doubled if the goal was not reached. RESULTS: LDL-C decreased by 27% and 38%, in the every-other-day (n = 15) and every-day (n = 15) groups, respectively, at 6 weeks. At 12 weeks, the LDL-C was reduced by 35% and 38% in the every-other-day and every-day groups, respectively (P =.49). The mean dose was 18 mg (9 mg/d) in the alternate-day group (n = 14) and 12 mg/d in the every-day group (n = 12) at the end of the 12 weeks (P =.001). CONCLUSIONS: Although higher doses of atorvastatin were used on alternate days, these results suggest that the alternate-day administration of atorvastatin can produce a reduction in LDL-C comparable to that of daily administration in patients with hypercholesterolemia, and yet provide some cost savings

Using tricyclic antidepressants in the elderly.

McCue RE.

*Clin Geriatr Med.* 1992 May; 8(2):323-34.

Only a few of the eight tricyclic antidepressants available today have been studied systematically in the elderly. Tertiary amine tricyclics such as amitriptyline and imipramine have been reported to be effective in depressed geriatric patients, but because of their potential for side effects, it is not advisable to use them in the elderly. Desipramine has a less toxic side effect profile, especially with respect to anticholinergic effects, but its efficacy has not been well studied. This does not mean, however, that it is not an effective drug for the elderly depressed. Nortriptyline is the tricyclic that has been the most studied. The results of those studies show that it should be recommended as an antidepressant for older patients. It is effective in both the acute and continuation treatment of depression in the elderly. As far as its use in maintenance treatment, the results are mixed but at this moment there is nothing with which to compare it. It has a favorable side effect profile: low anticholinergic activity; relatively few cardiac side effects, even in patients with preexisting cardiac disease; and relatively less orthostatic hypotension. Nortriptyline also has the virtue of an established therapeutic range for its steady-state plasma level. The role of its 10-hydroxy metabolite needs to be further explored, but when its contribution to efficacy and toxicity is better understood, it may be possible to use nortriptyline in a more precise and safe way in elderly patients. The bulk of evidence suggests, partly by default, that nortriptyline should probably be the tricyclic-of-first-choice in treating an elderly patient with major depression

Prescribing hormone replacement therapy for menopausal symptoms.

McNaghy SE.

*Ann Intern Med.* 1999 Oct 19; 131(8):605-16.

This paper addresses the clinical presentation of menopause, pretreatment assessment for hormone replacement therapy, benefits and risks of this treatment, common hormone replacement regimens and their side effects, and patient management. The case-based discussion focuses on the clinical management of a patient who is considering hormone replacement therapy for menopausal symptoms

.Melmon and Morrelli's Clinical Pharmacology: Basic Principles in Therapeutics.

Melmon KLMHFHBBNDW.

1993; Third Edition:- McGraw-Hill.

Efficacy and safety of b.i.d. doses of venlafaxine in a dose-response study.

Mendels J, Johnston R, Mattes J, et al.

*Psychopharmacol Bull.* 1993; 29(2):169-74.

In this study, 312 depressed outpatients received either placebo or one of three venlafaxine doses twice daily (b.i.d.) for up to 6 weeks. The total daily doses of venlafaxine were 25, 50-75, and 150-200 mg/day. Hamilton Rating Scale for Depression (HAM-D) and Montgomery-Asberg Depression Rating Scale (MADRS) total scores at Week 6 were significantly lower for the high-dose group than for the placebo group. A positive dose-response trend for the primary efficacy parameters was demonstrated as early as Week 1. Venlafaxine was well tolerated at all dose levels. The most common side effects of clinical interest were nausea and dry mouth. The frequency of nausea in the venlafaxine groups was essentially the same (25-29%), whereas the frequencies of dry mouth, somnolence, and sweating were dose related. The results indicate that b.i.d. doses of venlafaxine are safe and effective in treating depression

The dose effects of zolpidem on the sleep of healthy normals.

Merlotti L, Roehrs T, Koshorek G, et al.

*J Clin Psychopharmacol.* 1989 Feb; 9(1):9-14.

This study determined the dose effects of zolpidem in 12 healthy males with normal sleep patterns. Subjects spent 7 weeks, 3 consecutive nights per week, in the laboratory and had a 4-night washout between treatments. The first week was a screening and adaptation week. Then subjects received zolpidem (2.5, 5.0, 7.5, 10.0, or 20.0 mg) or placebo on the first two nights for each of the next 6 consecutive weeks. Treatments were organized in a Latin square design and administered in a double-blind fashion. On the third night of each treatment, subjects always received placebo. The 5.0 mg and larger doses of zolpidem significantly decreased latency to persistent sleep and wake before sleep. Sleep maintenance measures were not affected by zolpidem. The 7.5 mg and higher doses of zolpidem significantly increased total sleep time. The only significant sleep stage effect was a decrease in percent of rapid eye movement sleep at only the 20 mg dose. No consistent discontinuation effects were found. Zolpidem was hypnotically active at doses as low as 5.0 and 7.5 mg, and sleep stage effects occurred only at the 20 mg dose, thus separating the dose range of hypnotic and sleep stage effects

Management of drug therapy in the elderly.

Montamat SC, Cusack BJ, Vestal RE.

*N Engl J Med.* 1989 Aug 3; 321(5):303-9.

Time to act on drug safety.

Moore TJ, Psaty BM, Furberg CD.

*JAMA.* 1998 May 20; 279(19):1571-3.

Diclofenac sodium (Voltaren) and indomethacin in the ambulatory treatment of rheumatoid arthritis: a double-blind multicentre study.

Mutru O, Penttila M, Pesonen J, et al.

*Scand J Rheumatol Suppl.* 1978;(22):51-6.

In a double-blind crossover trial conducted on a multicentre basis, 109 patients with "classic" or "definite" rheumatoid arthritis were treated for two weeks with diclofenac sodium (Voltaren, 25 mg t.i.d.) and indomethacin (25 mg t.i.d). Both drugs led to a clear-cut decrease in morning stiffness, as well as to a significant improvement in pain at rest and on movement. In these respects no significant difference between the two-drugs was observed. As regards their effect on status of rheumatoid condition, however, a trend towards a significant improvement was discernible, in the investigator's opinion, only in response to diclofenac sodium. "Unwanted effects" were mentioned by 25 patients before the trial, by 31 during treatment with diclofenac sodium, and by 33 during treatment with indomethacin. While the patients were receiving indomethacin, five of them discontinued treatment on account of side effects (headache in three cases, headache and tiredness in one case, and an allergic skin reaction in one case) and one of them, who complained of headache, lowered the dosage; treatment with diclofenac sodium was discontinued because of side effects by only one patient, who had developed an allergic skin reaction

Reduction of LDL cholesterol by 25% to 60% in patients with primary hypercholesterolemia by atorvastatin, a new HMG-CoA reductase inhibitor.

Nawrocki JW, Weiss SR, Davidson MH, et al.

*Arterioscler Thromb Vasc Biol.* 1995 May; 15(5):678-82.

This 6-week, double-blind clinical trial evaluated lipid parameter responses to different dosages of atorvastatin in patients with primary hypercholesterolemia. Atorvastatin is a new 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor under development. After completing an 8-week placebo-baseline dietary phase, 81 patients were randomly assigned to receive either placebo or 2.5, 5, 10, 20, 40, or 80 mg atorvastatin once daily for 6 weeks. Plasma LDL cholesterol reductions from baseline were dose related, with 25% to 61% reduction from the minimum dose to the maximum dose of 80 mg atorvastatin once a day. Plasma total cholesterol and apo B reductions were also dose related. Previously, reductions in LDL cholesterol of the magnitude observed in this study have been seen only with combination drug therapy. In this study, atorvastatin was well

tolerated by hyperlipidemic patients, had an acceptable safety profile, and provided greater reduction in cholesterol than other previously reported HMG-CoA reductase inhibitors

Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. .

NCEP.

*JAMA*. 2001; 285(19):248697.

Efficacy and safety of cerivastatin, 0.2 mg and 0.4 mg, in patients with primary hypercholesterolaemia: a multinational, randomised, double-blind study. Cerivastatin Study Group.

Ose L, Luurila O, Eriksson J, et al.

*Curr Med Res Opin*. 1999; 15(3):228-40.

Elevated serum cholesterol level is a key risk factor for cardiovascular morbidity and mortality. Cerivastatin is a highly effective lipid-lowering agent currently licensed at doses of 0.1, 0.2, 0.3 and 0.4 mg. This was a multicentre, randomised, double-blind, parallel-group study comparing the efficacy and safety of cerivastatin 0.4 mg/day with that of cerivastatin 0.2 mg/day in patients with primary hypercholesterolaemia. There was a six-week placebo run-in phase followed by a 24-week active treatment phase. A total of 494 patients were randomised to receive cerivastatin 0.4 mg (n = 332) or 0.2 mg (n = 162). Per-protocol (PP) analysis revealed that mean low-density lipoprotein cholesterol (LDL-C) level decreased by 38.4 +/- 0.7% from baseline in the 0.4 mg group, compared with a decrease of 31.5 +/- 0.9% in the 0.2 mg group (p < 0.0001). There was a significant gender difference in the 0.4 mg group: LDL-C decreased by 44.4 +/- 8.9% in women, compared with a decrease of 37.0 +/- 0.9% in men (p < 0.046). In the PP group as a whole, total cholesterol decreased by 26.0 +/- 0.5% from baseline in the 0.4 mg group, compared with a decrease of 21.6 +/- 0.7% in the 0.2 mg group (p < 0.0001). Both doses were well tolerated; only eight (2.4%) patients in the 0.4 mg group and five (3.1%) patients in the 0.2 mg group withdrew owing to adverse events. Cerivastatin 0.2 mg/day and 0.4 mg/day was found to lower low-density lipoprotein cholesterol and total cholesterol levels in a dose-dependent manner, with both doses exhibiting a good safety profile

Efficacy and safety of fluvastatin in women with primary hypercholesterolaemia 5.

Peters TK, Muratti EN, Mehra M.

*Drugs*. 1994; 47 Suppl 2:64-72.

Women with primary hypercholesterolaemia are often considered for lipid-lowering drug therapy at a later age than men. With regard to the prevention of cardiovascular morbidity, women can expect to receive the same benefits from lipid-lowering treatment as men. Thus, it is of interest to evaluate the efficacy, safety and tolerability of the new lipid-lowering agent fluvastatin in women. A retrospective analysis was made on the basis of data from controlled clinical trials in which 1815 patients were treated with fluvastatin at a daily dose of > or = 20 mg, and 783 patients received placebo. 782 of the fluvastatin-treated patients (43.1%) and 315 patients on placebo (40.2%) were women. Within these groups, 577 patients (73.8%) treated with fluvastatin and 183 patients receiving placebo (78.4%) were at least 50 years of age. The effect of fluvastatin 40 mg/day on low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol was more favourable in women than in men. In women, the change from baseline was -26.7% for LDL cholesterol and 5.3% for HDL cholesterol. In men, the equivalent changes from baseline were -23.8% and 4.0%, respectively. All changes from baseline were highly significant (p < 0.001). Fluvastatin lowered triglycerides to a similar extent in women and men (7.1% vs 6.9%, respectively). More women than men experienced a confirmed increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) when receiving fluvastatin. (ABSTRACT TRUNCATED AT 250 WORDS)

Top 10 drugs of 2001.

Pharmacy Times.

*Pharmacy Times*. 2002.Apr 68(4):105.

Pharmacokinetics of antidepressants: why and how they are relevant to treatment.

Preskorn SH.

The pharmacokinetics of antidepressants are reviewed with special emphasis on clinical applicability. There are substantial pharmacokinetic differences among the five major classes. Pharmacokinetic differences between members of a specific class are usually modest except for serotonin selective reuptake inhibitors. Between members of this class pharmacokinetic differences are the major distinguishing variables and have clinically important consequences

Effect of risperidone on behavioral and psychological symptoms and cognitive function in dementia.

Rainer MK, Masching AJ, Ertl MG, et al.

*J Clin Psychiatry.* 2001 Nov; 62(11):894-900.

**AIMS:** This open-label study examined the efficacy and tolerability of risperidone in the treatment of aggression, agitation, and psychotic symptoms in dementia. The influence of risperidone on cognitive function was also assessed under conditions reflecting normal, daily clinical care. **METHOD:** A total of 34 hospital inpatients and outpatients (mean age = 76 years) with DSM-IV dementia disorders were treated with flexible doses of risperidone (0.5-2 mg/day) for 8 weeks. Assessments, conducted at baseline and after weeks 4 and 8, included the Clinical Global Impressions scale (CGI) and Neuropsychiatric Inventory (NPI) ratings. Cognitive function assessments included the Mini-Mental State Examination (MMSE) and specific measures of cognition (Age Concentration Test [AKT] and Brief Syndrome Test [SKT]). Frequency of extrapyramidal symptoms (EPS) was measured according to the Extrapyramidal Symptom Rating Scale (ESRS). **RESULTS:** At the end of the study, 50% of patients (N = 17) were receiving risperidone, 1 mg/day. 18% (N = 6) were receiving 0.5 mg/day, and 32% (N = 11) received > 1 mg/day (mean dose at endpoint = 1.1 mg/day). An improvement in symptoms, as measured by the CGI-Global Impression of Change scale, was reported for 82% of patients (N = 28) (59% [N = 20] much or very much improved). The frequency and severity of delusions, hallucinations, agitation/aggression, and irritability decreased as measured by the NPI. Multiplication of frequency and severity scores revealed a significant decline during the course of treatment ( $p < .001$ , end of study vs. baseline). Caregiver responses on the NPI also showed an improvement, with the mean +/- SD total score decreasing from 24.2 +/- 7.3 at baseline to 21.2 +/- 6.3 at study end ( $p = .002$ ). MMSE, AKT, and SKT results indicated that there was no decrease in cognitive function during the study. Risperidone treatment was well tolerated, and no clinically relevant changes in EPS, vital signs, or weight were detected. **CONCLUSION:** During treatment with low-dose risperidone, behavioral and psychological symptoms improved overall in 34 patients with dementia, and cognitive function was maintained throughout the treatment period

Conn's Current Therapy.

Rakel RE.

1993;

57 deaths in Britain associated with Zyban.

Reuters Health.

*Reuters Health.* 2002 Jan 1;

Medical journals act to limit drug firms' influence.

Reuters Health.

*Reuters Health.* 2001 Sep 10

Nefazodone and imipramine in major depression: a placebo-controlled trial.

Rickels K, Schweizer E, Clary C, et al.

*Br J Psychiatry.* 1994 Jun; 164(6):802-5.

Nefazodone is a phenylpiperazine antidepressant with 5-HT<sub>2</sub> antagonism and 5-HT reuptake inhibition. Two hundred and eighty-three out-patients with a diagnosis of DSM-III-R major depression of at least one-month duration (65% ill for over 6 months), and a mean score of 24 on the 17-item Hamilton Rating Scale for Depression (HRSD), were randomised to treatment with nefazodone, imipramine, or placebo. The double-blind treatment period was 8 weeks in duration. Nefazodone's antidepressant efficacy was comparable with imipramine's, with both drug treatments significantly better than placebo in a variety of outcome

measures. For example, after 8 weeks of therapy, 78% of nefazodone and 83% of imipramine but only 55% of placebo patients ( $P < 0.01$ ) were globally much or very much improved. Nefazodone was better tolerated than imipramine, with fewer drop-outs and a lower incidence of side-effects during treatment

Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events.

Ridker PM, Rifai N, Rose L, et al.

*N Engl J Med.* 2002 Nov 14; 347(20):1557-65.

**BACKGROUND:** Both C-reactive protein and low-density lipoprotein (LDL) cholesterol levels are elevated in persons at risk for cardiovascular events. However, population-based data directly comparing these two biologic markers are not available. **METHODS:** C-reactive protein and LDL cholesterol were measured at base line in 27,939 apparently healthy American women, who were then followed for a mean of eight years for the occurrence of myocardial infarction, ischemic stroke, coronary revascularization, or death from cardiovascular causes. We assessed the value of these two measurements in predicting the risk of cardiovascular events in the study population. **RESULTS:** Although C-reactive protein and LDL cholesterol were minimally correlated ( $r=0.08$ ), base-line levels of each had a strong linear relation with the incidence of cardiovascular events. After adjustment for age, smoking status, the presence or absence of diabetes mellitus, categorical levels of blood pressure, and use or nonuse of hormone-replacement therapy, the relative risks of first cardiovascular events according to increasing quintiles of C-reactive protein, as compared with the women in the lowest quintile, were 1.4, 1.6, 2.0, and 2.3 ( $P<0.001$ ), whereas the corresponding relative risks in increasing quintiles of LDL cholesterol, as compared with the lowest, were 0.9, 1.1, 1.3, and 1.5 ( $P<0.001$ ). Similar effects were observed in separate analyses of each component of the composite end point and among users and nonusers of hormone-replacement therapy. Overall, 77 percent of all events occurred among women with LDL cholesterol levels below 160 mg per deciliter (4.14 mmol per liter), and 46 percent occurred among those with LDL cholesterol levels below 130 mg per deciliter (3.36 mmol per liter). By contrast, because C-reactive protein and LDL cholesterol measurements tended to identify different high-risk groups, screening for both biologic markers provided better prognostic information than screening for either alone. Independent effects were also observed for C-reactive protein in analyses adjusted for all components of the Framingham risk score. **CONCLUSIONS:** These data suggest that the C-reactive protein level is a stronger predictor of cardiovascular events than the LDL cholesterol level and that it adds prognostic information to that conveyed by the Framingham risk score

Optimising drug treatment for elderly people: the prescribing cascade.

Rochon PA, Gurwitz JH.

*BMJ.* 1997 Oct 25; 315(7115):1096-9.

Age- and gender-related use of low-dose drug therapy: the need to manufacture low-dose therapy and evaluate the minimum effective dose.

Rochon PA, Anderson GM, Tu JV, et al.

*J Am Geriatr Soc.* 1999 Aug; 47(8):954-9.

**OBJECTIVES:** Low-dose drug therapy is promoted as a way to maximize benefit and minimize adverse drug effects when prescribing for older adults. This population-based study evaluates the age and sex-related use of two common therapies: thiazide diuretics, where evidence supports the use of low-dose therapy, and beta-blockers, where trials have not evaluated the minimum effective dose. **DESIGN:** Using linked administrative databases we identified all of the 120,613 persons dispensed a thiazide diuretic therapy and 12,908 myocardial infarction survivors dispensed beta-blocker therapy in Canada's largest province. We used logistic regression models to study the association of age and sex with dispensing of low-dose thiazide diuretic and beta-blocker therapy at doses lower than evaluated in trials. **RESULTS:** Of 120,613 older people dispensed a thiazide diuretic, 32,372 (26.8%) were dispensed a low dose. Patients 85 years of age or older, relative to the youngest group, were 30% more likely to be dispensed low-dose therapy (OR=1.31; 95% CI, 1.27 to 1.36;  $P < .001$ ). Women were 8% more likely than men to be dispensed a low-dose thiazide diuretic (OR="1.08;" 95% CI, 1.05 to 1.11;  $P < .001$ ). Of 10,991 myocardial infarction survivors dispensed atenolol, metoprolol, propranolol, or timolol, 9458 (86.1%) were dispensed a lower-than-evaluated dose. Patients 85 years of age or older, relative to those in the youngest group, were more than twice as likely to be dispensed a lower-than-evaluated beta-blocker therapy dose (OR="2.28;" 95% CI, 1.74 to 3.04;  $P < .001$ ). No difference was noted in the use of beta-blocker therapy dose by sex (OR="1.0;" 95% CI, .89 to 1.15;  $P = ".95$ )." **CONCLUSIONS:** Low-dose thiazide diuretic therapy prescribed widely to older people, particularly those of advanced age and women. The vast majority of myocardial infarction survivors were dispensed beta-blocker therapy at lower-than-evaluated doses. These findings highlight the need to manufacture low-dose thiazide diuretic therapy and to evaluate the minimum effective dose of beta-blocker therapy

Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial.

Rossouw JE, Anderson GL, Prentice RL, et al.

*JAMA*. 2002 Jul 17; 288(3):321-33.

**CONTEXT:** Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain. **OBJECTIVE:** To assess the major health benefits and risks of the most commonly used combined hormone preparation in the United States. **DESIGN:** Estrogen plus progestin component of the Women's Health Initiative, a randomized controlled primary prevention trial (planned duration, 8.5 years) in which 16608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited by 40 US clinical centers in 1993-1998. **INTERVENTIONS:** Participants received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n = 8506) or placebo (n = 8102). **MAIN OUTCOMES MEASURES:** The primary outcome was coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome. A global index summarizing the balance of risks and benefits included the 2 primary outcomes plus stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes. **RESULTS:** On May 31, 2002, after a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial of estrogen plus progestin vs placebo because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits. This report includes data on the major clinical outcomes through April 30, 2002. Estimated hazard ratios (HRs) (nominal 95% confidence intervals [CIs]) were as follows: CHD, 1.29 (1.02-1.63) with 286 cases; breast cancer, 1.26 (1.00-1.59) with 290 cases; stroke, 1.41 (1.07-1.85) with 212 cases; PE, 2.13 (1.39-3.25) with 101 cases; colorectal cancer, 0.63 (0.43-0.92) with 112 cases; endometrial cancer, 0.83 (0.47-1.47) with 47 cases; hip fracture, 0.66 (0.45-0.98) with 106 cases; and death due to other causes, 0.92 (0.74-1.14) with 331 cases. Corresponding HRs (nominal 95% CIs) for composite outcomes were 1.22 (1.09-1.36) for total cardiovascular disease (arterial and venous disease), 1.03 (0.90-1.17) for total cancer, 0.76 (0.69-0.85) for combined fractures, 0.98 (0.82-1.18) for total mortality, and 1.15 (1.03-1.28) for the global index. Absolute excess risks per 10 000 person-years attributable to estrogen plus progestin were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10 000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the global index was 19 per 10 000 person-years. **CONCLUSIONS:** Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD

Variability in Drug Therapy: Description, Estimation, and Control 1985 (A Sandoz Workshop). : .

Rowland MSLSJ.

1985;

Application of an individually predicted dosage of amitriptyline to the treatment of depression.

Roy D, Dawling S.

*Int Clin Psychopharmacol*. 1987 Oct; 2(4):307-15.

The treatment of depressed patients with a fixed dose of amitriptyline is compared to treatment with an individualized dose calculated by means of a simple pharmacokinetic test. Clinical response and the development of side-effects are compared between the two groups of patients. Although the numbers in the groups were small, the clinical results lend little support to the concept of a therapeutic range of plasma drug concentrations for amitriptyline, and none of the plasma concentrations was high enough to produce serious toxic effects. No obvious clinical advantage was observed in the predicted dose treatment group as assessed by a reduction in depression ratings. The dose prediction test did however more than halve the variance in blood drug concentrations, and its usefulness in preventing high and potentially toxic concentrations is indisputable

A clinical and psychometric evaluation of flurazepam.

Salkind MR, Silverstone T.

*Br J Clin Pharmacol*. 1975 Jun; 2(3):223-6.

1 The efficacy of flurazepam (15 mg or 30 mg) as a hypnotic, and the residual effects of each dose were compared with placebo

in a double-blind cross-over trial involving thirty patients in a general practice setting. Patients received each medication for one week. Daily self-ratings of onset, duration and quality of sleep, together with reports of any untoward effects were made. At the end of each period of medication psychomotor tests (reaction time, pursuit rotor, tapping speed) were administered at 09.00 hours. 2 Both doses of flurazepam were significantly more effective than placebo in inducing sleep, improving the quality of sleep and extending its duration. 3 'Hangover' effects were marked following 30 mg, but not after flurazepam (15 mg). Flurazepam (30 mg, but not 15 mg) significantly impaired performance on the pursuit rotor test and tapping speed. Flurazepam thus appears to be an effective hypnotic drug with the optimum dose for use in general practice being 15 mg at night

Practical considerations in the pharmacologic treatment of depression and anxiety in the elderly.

Salzman C.

*J Clin Psychiatry.* 1990 Jan; 51 Suppl:40-3.

The author discusses four topics: (1) Age-related alterations in central nervous system function predispose elderly patients to increased risk of psychotropic drug toxicity. (2) Age-related alterations in psychotropic drug pharmacokinetics lead to decreased metabolism, increased volume of distribution, and decreased clearance. (3) Treatment of depression in the elderly with a special focus on selection of drugs and toxicity. Four classes of drugs are reviewed: cyclic antidepressants, atypical antidepressants, monoamine oxidase inhibitors, and stimulants. and (4) Treatment of anxiety. Recommendations for benzodiazepine and buspirone use are given, and benzodiazepine toxicity in the elderly is reviewed in detail

Low bedtime doses of H<sub>2</sub>-receptor antagonists for acute treatment of duodenal ulcer.

Savarino V, Mela GS, Zentilin P, et al.

*Dig Dis Sci.* 1989 Jul; 34(7):1043-6.

Twenty-four-hour intragastric acidity was measured continuously over five separate occasions in 15 patients with healed duodenal ulcers. They were randomized to receive either placebo, cimetidine 800 mg, ranitidine 150 mg, famotidine 20 mg, or nizatidine 150 mg, given at 2200 hr in double-blind fashion. All H<sub>2</sub>-receptor blockers were more effective than placebo in suppressing both circadian (P less than 0.05-P less than 0.01) and nocturnal (P less than 0.002) gastric acidity, while there was no significant differences between the effects of the four active drugs in the same time periods. The percentage of nocturnal acid inhibition (2300-0800 hr) over placebo in terms of H<sup>+</sup> values was virtually 100% with all active treatments. The effect on daytime (0800-1700 hr) and evening (1700-2300 hr) acidity of both placebo and the four H<sub>2</sub>-receptor antagonists was similar. Therefore, in the above doses H<sub>2</sub>-receptor blockers guarantee overnight anacidity to a similar degree and cause the physiological buffering of daily meals on gastric acidity to be fully exploited. Furthermore, the reducing effect of daily meals on drug action can be prevented. Since strong acid suppression strictly confined to the nocturnal period has been shown to be closely correlated with the highest ulcer healing rates, it is suggested that single low bedtime doses of H<sub>2</sub>-receptor antagonist should be evaluated in the acute treatment of duodenal ulcer

Recent studies on selective serotonergic antidepressants: trazodone, fluoxetine, and fluvoxamine.

Schatzberg AF, Dessain E, O'Neil P, et al.

*J Clin Psychopharmacol.* 1987 Dec; 7(6 Suppl):44S-9S.

In recent years, the role of serotonin in the pathophysiology of depressive disorders has been intensively studied. These studies have been complemented by the development of newer antidepressant agents that exert specific effects on serotonin systems. This paper reviews the pharmacology of these newer compounds and contrasts it with those of the standard tricyclic antidepressants. The current status of various serotonergic agents is discussed. Results are reviewed from recent double-blind studies comparing three compounds (trazodone, fluoxetine, and fluvoxamine) to a standard tricyclic antidepressant. Relative efficacy, dropout rates, optimal dosages, and side effects are emphasized. Data from studies on trazodone and fluoxetine suggest that lower dosages may prove as effective (if not more effective) than very high dosages. Implications of these data are discussed. Side effects of fluoxetine and fluvoxamine include primarily nausea, weight loss, insomnia, and anxiety. Possible application of specific serotonin reuptake blockers in the treatment of obsessive-compulsive disorder and in the reduction of alcohol consumption is also reviewed

Dosing strategies for antidepressant agents.

Schatzberg AF.

In this paper, the author reviews the dosing strategy for each major class of antidepressant drugs. The long-accepted strategy of moving from low to high dosages may need to be revised when the newer serotonergic agents are used to treat depressed patients. Evidence indicates that these drugs may be both better tolerated and more effective at lower dosages. Several studies in support of this hypothesis are reviewed. Possible dosing strategies of serotonergic agents, such as fluoxetine, in the treatment of obsessive compulsive disorder, obesity, and other nondepressive disorders, are also discussed

A national survey of provisions in clinical-trial agreements between medical schools and industry sponsors.

Schulman KA, Seils DM, Timbie JW, et al.

*N Engl J Med.* 2002 Oct 24; 347(17):1335-41.

**BACKGROUND:** Concerned about threats to the integrity of clinical trials in a research environment increasingly controlled by private interests, the International Committee of Medical Journal Editors (ICMJE) has issued revised guidelines for investigators' participation in the study design, access to data, and control over publication. It is unclear whether research conducted at academic institutions adheres to these new standards. **METHODS:** From November 2001 through January 2002, we interviewed officials at U.S. medical schools about provisions in their institutions' agreements with industry sponsors of multicenter clinical trials. A subgroup of the respondents were also asked about coordinating-center agreements for such trials. **RESULTS:** Of the 122 medical schools that are members of the Association of American Medical Colleges, 108 participated in the survey. The median number of site-level agreements executed per institution in the previous year was 103 (interquartile range, 50 to 210). Scores for compliance with a wide range of provisions--from ensuring that authors of reports on multicenter trials have access to all trial data (1 percent [interquartile range, 0 to 21]) to addressing the plan for data collection and monitoring (10 percent [interquartile range, 1 to 50])--demonstrated limited adherence to the standards embodied in the new ICMJE guidelines. Scores for coordinating-center agreements were somewhat higher for most survey items. **CONCLUSIONS:** Academic institutions routinely engage in industry-sponsored research that fails to adhere to ICMJE guidelines regarding trial design, access to data, and publication rights. Our findings suggest that a reevaluation of the process of contracting for clinical research is urgently needed

The effects of ibuprofen in the treatment of dysmenorrhea.

Shapiro SSDK.

*Curr Ther Res.* 1981; 30(3):32734.

Statins: grossly overprescribed for cholesterol and underprescribed for internal inflammation.

Sinatra S.

*The Sinatra Health Report.* 2002 Sep 1;

Clinical pharmacology of antidepressant drugs: pharmacogenetics.

Sjoqvist F, Bertilsson L.

*Adv Biochem Psychopharmacol.* 1984; 39:359-72.

There are marked interindividual differences in  $C_{ss}$  of tricyclic antidepressants. These are due mainly to corresponding differences in the rate of elimination of the drugs and hence in drug oxidation. Twin, family, and cross-over studies with NT and DMI show that their kinetics ( $C_{ss}$ ,  $K_{el}$ , and  $V_d$ ) are controlled mainly by genetic factors (in drug-free individuals). Slow hydroxylators are at risk of developing excessive plasma concentrations of NT and DMI when given per se or when formed from the tertiary amines AT and imipramine. Classic antidepressants have fairly well established concentration-effect curves in endogenous depression. Severe toxicity usually occurs at supratherapeutic plasma levels and might be prevented by tailoring the dosage according to the individual's drug hydroxylating capacity. Monitoring drug plasma levels is particularly relevant in slow hydroxylators. There is a strong association between an individual's ability to hydroxylate NT and DMI and his D hydroxylation phenotype. The ratios between D and 4-OH-D in urine after a single oral dose are bimodally distributed in the population (polymorphism), with 3 to 10% being slow hydroxylators and the remainder rapid hydroxylators. Indices of NT-hydroxylation do not sharply distinguish the two phenotypes. The D metabolic index will predict the patient's capacity to hydroxylate NT and DMI and hence  $C_{ss}$  during therapy. Possibly similar hydroxylases are involved in the 4-hydroxylation of debrisoquine, in the stereospecific E-10-hydroxylation of NT, and in the 2-hydroxylation of DMI. By contrast demethylation of AT

(and probably other tertiary tricyclics) does not significantly correlate to debrisoquine hydroxylation. The increasing knowledge of the clinical pharmacokinetics of tricyclic antidepressants is a distinct advantage over that of the new generation of antidepressants, where little is known about concentration-effect relationships and factors governing their rate of metabolism

Does digoxin provide additional hemodynamic and autonomic benefit at higher doses in patients with mild to moderate heart failure and normal sinus rhythm?

Slatton ML, Irani WN, Hall SA, et al.

*J Am Coll Cardiol.* 1997 May; 29(6):1206-13.

**OBJECTIVES:** This study sought to examine the hemodynamic and autonomic dose response to digoxin. **BACKGROUND:** Previous studies have demonstrated an increase in contractility and heart rate variability with digitalis preparations. However, little is known about the dose-response to digoxin, which has a narrow therapeutic window. **METHODS:** Nineteen patients with moderate heart failure and a left ventricular ejection fraction < 0.45 were studied hemodynamically using echocardiography and blood pressure at baseline and after 2 weeks of low dose (0.125 mg daily) and 2 weeks of moderate dose digoxin (0.25 mg daily). Loading conditions were altered with nitroprusside at each study. Autonomic function was studied by assessing heart rate variability on 24-h Holter monitoring and plasma norepinephrine levels during supine rest. **RESULTS:** Low dose digoxin provided a significant increase in ventricular performance, but no further increase was seen with the moderate dose. Low dose digoxin reduced heart rate and increased heart rate variability. Moderate dose digoxin produced no additional increase in heart rate variability or reduction in sympathetic activity, as manifested by heart rate, plasma norepinephrine or low frequency/high frequency power ratio. In addition, we did not find that either low or moderate dose digoxin increased parasympathetic activity. **CONCLUSIONS:** We conclude that moderate dose digoxin provides no additional hemodynamic or autonomic benefit for patients with mild to moderate heart failure over low dose digoxin. Because higher doses of digoxin may predispose to arrhythmogenesis, lower dose digoxin should be considered in patients with mild to moderate heart failure

DTC .

Smith DL.

*DTC Perspectives.* 2002.Jan

Adverse drug reactions causing hospital admission in an elderly population: experience with a decision algorithm.

Smucker WD, Kontak JR.

*J Am Board Fam Pract.* 1990 Apr; 3(2):105-9.

An adverse drug reaction (ADR) decision algorithm was used in the review of 100 consecutive hospital admissions of elderly patients cared for by family physicians. The algorithm is a valid methodologic alternative to using pharmacological experts for verification of an ADR. In this study, the algorithm was easily applied by family physicians, and the results were similar to those reported by expert clinical pharmacologists. Nine percent of our elderly patients' hospital admissions were caused by ADRs that were due to usual doses of medications commonly prescribed for elderly patients. Average age of patients and number of medications were similar for persons with and without ADRs. The algorithm can be useful to physicians investigating ADRs for clinical research, physician education, quality assurance, and improved patient care

The Pill: 30 Years of Safety Concerns.

Snider S.

190.Dec

Troglitazone in type II diabetes mellitus.

Sparano N, Seaton TL.

*Pharmacotherapy.* 1998 May; 18(3):539-48.

Troglitazone, a new antihyperglycemic agent, is approved for use alone, with oral sulfonylureas, or with insulin in the treatment of type II diabetes mellitus. Rather than stimulating insulin secretion, it enhances insulin sensitivity. Potential advantages of troglitazone over oral sulfonylureas include decreased endogenous insulin concentrations, decreased exogenous insulin

requirements, reduced hypoglycemic risk, and convenient once/day administration. The effect on morbidity and mortality from lowering endogenous and exogenous insulin concentrations remains to be determined. Troglitazone also has potential disadvantages. It induces cytochrome P450 isoenzyme 3A4, although few drug interactions have been identified to date. Serum transaminases must be monitored routinely because of rarely reported cases of idiosyncratic hepatocellular injury. In addition, the cost of troglitazone is much higher than that of other oral antihyperglycemic agents or insulin. Given the available information, troglitazone has limited benefit over oral sulfonylureas or metformin as monotherapy or in combination with oral sulfonylureas. Until additional combination and comparative studies have been done, the agent should be reserved for patients with poor glycemic control receiving high daily doses of insulin

Comparative efficacy and tolerability of 5 and 10 mg simvastatin and 10 mg pravastatin in moderate primary hypercholesterolemia. Simvastatin Pravastatin European Study Group.

Steinhagen-Thiessen E.

*Cardiology*. 1994; 85(3-4):244-54.

Simvastatin and pravastatin, two 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, were compared in a multinational, randomized, double-blind trial. Patients demonstrating moderate hypercholesterolemia after 10 weeks on a lipid-lowering diet received 6 weeks of treatment with 5 mg/day simvastatin (n = 143) or 10 mg/day pravastatin (n = 138); the simvastatin dose was increased to 10 mg for an additional 6 weeks while the pravastatin dose remained at 10 mg. When administered at lower or equivalent daily doses, simvastatin was significantly more effective than pravastatin in reducing total and low-density lipoprotein (LDL) cholesterol. Reductions in plasma total and LDL cholesterol were significantly greater with 5 mg simvastatin (16 and 23%) compared to 10 mg pravastatin (12 and 18%;  $p < \text{or} = "0.01"$ .) The efficacy of 10 mg simvastatin in lowering these lipid parameters was also superior (19 vs. 11% and 27 vs. 17%, respectively;  $p < \text{or} = "0.01"$ .) At 6 and 12 weeks, a significantly higher percentage of simvastatin patients (45 and 59%, respectively) achieved a desirable LDL cholesterol level of  $< 130 \text{ mg/dl}$  ( $< 3.4 \text{ mmol/l}$ ) compared to pravastatin patients (32-33%;  $p < \text{or} = "0.05"$ .) Both drugs were well tolerated and had comparable safety profiles

Further experience with ibuprofen in the treatment of arthritis.

Thompson M, Bell D.

*Rheumatol Phys Med*. 1970; 10:Suppl-3.

Efficacy and safety of fexofenadine in fall seasonal allergic rhinitis.

Tinkelman DFMBEea.

*J Allergy Clin Immunol*. 1996; 97(1):1009.

Dose-response of simvastatin in primary hypercholesterolemia.

Tuomilehto J, Guimaraes AC, Kettner H, et al.

*J Cardiovasc Pharmacol*. 1994 Dec; 24(6):941-9.

In an 8-week, placebo-controlled multicenter study, the efficacy of dose levels of simvastatin 2.5, 5, 10, 20, and 40 mg was evaluated in 166 patients with hypercholesterolemia, of whom 163 completed the trial. The entry criteria were serum total cholesterol (TCHOL) between 6.2 and 7.8 mM and low-density lipoprotein (LDL) cholesterol between 4.3 and 50 mM on a standard diet and after the 2-week run-in period of placebo treatment. Mean percentage changes in serum lipids in each simvastatin-treated group from baseline were statistically significant. Of treated patients, 0% (placebo), 11% (2.5 mg), 7% (5 mg), 33% (10 mg), 42% (20 mg) and 55% (40 mg) had at least 40% reduction from baseline LDL cholesterol value. After 8 weeks of treatment, 0% (placebo), 11% (2.5 mg), 25% (5 mg), 26% (10 mg), 31% (20 mg), and 55% (40 mg) of patients treated reached a TCHOL level of or = 5 mg moderately increased HDL cholesterol and reduced serum TG. Simvastatin therapy resulted in major improvement in serum lipoprotein profile, particularly at higher doses

Drug Information for the Health Care Professional 1994.

United States Pharmacopeia Drug Information (USP DI).

1994;

Speculations about mortality trends from venous thromboembolic disease in England and Wales and their relation to the pattern of oral contraceptive usage.

Vessey MP, Inman WH.

*J Obstet Gynaecol Br Commonw.* 1973 Jun; 80(6):562-6.

Gifts to physicians from the pharmaceutical industry.

Vollmann J.

*JAMA.* 2000 May 24; 283(20):2656-8.

Hepatic dysfunction associated with troglitazone.

Watkins PB, Whitcomb RW.

*N Engl J Med.* 1998 Mar 26; 338(13):916-7.

Efficacy of a continuous estrogen-progestin regimen in the menopausal patient.

Weinstein L.

*Obstet Gynecol.* 1987 Jun; 69(6):929-32.

The major concern with the use of unopposed estrogen is its neoplastic effect on the endometrium. Progestins used to oppose the estrogen may be associated with vaginal bleeding and reversal of estrogen's protective changes in serum lipoprotein concentrations. A study was performed in which all postmenopausal women received conjugated equine estrogen for days 1-28; with group I receiving 2.5 mg medroxyprogesterone acetate for days 1-28, group II receiving 5 mg medroxyprogesterone acetate for days 1-28, and group III receiving 5 mg medroxyprogesterone acetate for days 17-28. Pre- and postdrug evaluations of the endometrium revealed atrophic changes after therapy with continuous combined estrogen-progestin. Pre- and poststudy evaluation of serum lipoprotein concentrations demonstrated significant declines in cholesterol and low-density lipoprotein cholesterol within groups I and III, and no change in group II. All patients kept a weekly diary recording any vaginal bleeding or change in vasomotor symptoms. The results suggest that a continuous regimen of 0.625 mg conjugated equine estrogen with 2.5 mg medroxyprogesterone acetate is beneficial as a primary hormonal replacement therapy for the postmenopausal patient

Low-dose fluoxetine therapy for depression.

Wernicke JF, Dunlop SR, Dornseif BE, et al.

*Psychopharmacol Bull.* 1988; 24(1):183-8.

Low-dose fluoxetine therapy for depression.

Wernicke JF, Dunlop SR, Dornseif BE, et al.

*Psychopharmacol Bull.* 1988; 24(1):183-8.

High-density lipoprotein cholesterol and triglyceride response with simvastatin versus atorvastatin in familial hypercholesterolemia.

Wierzbicki AS, Lumb PJ, Chik G, et al.

*Am J Cardiol.* 2000 Sep 1; 86(5):547-9, A9.

The clinical and biochemical determinants of high-density lipoprotein (HDL) and triglyceride response to simvastatin and atorvastatin were assessed in 150 patients with severe hyperlipidemia treated in a randomized open-trial format design. Triglyceride reduction was only dependent on HDL:apolipoprotein A1, change in apolipoprotein B, and dose response, whereas

an increase in HDL was dependent on initial LDL, change in LDL or dose response, and therapy with simvastatin

Medications and older adults. 997 Sep/Oct:).

Williams RD.

*FDA Consumer Magazine*. 1997.Sep 31(6)

Medications and older adults.

Williams RD.

*FDA Consumer Magazine*. 1997.Sep

Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs.

Wolfe MM, Lichtenstein DR, Singh G.

*N Engl J Med*. 1999 Jun 17; 340(24):1888-99.

Worst Pills, Best Pills II: The Older Adult's Guide to Avoiding Drug-Induced Death or Illness.

Wolfe SMHRE.

1993; .

Efficacy and safety of a new cholesterol synthesis inhibitor, atorvastatin, in comparison with simvastatin and pravastatin, in subjects with hypercholesterolemia.

Wolffenbuttel BH, Mahla G, Muller D, et al.

*Neth J Med*. 1998 Apr; 52(4):131-7.

**BACKGROUND:** High levels of total and LDL-cholesterol are associated with an increased risk of atherosclerotic vascular disease. Lowering of serum cholesterol levels by pharmacologic intervention with inhibitors of cholesterol synthesis, the so-called statins, reduces the incidence of cardiovascular events in subjects with and without atherosclerotic manifestations. In a 16-week, multicenter, randomized, open-label cross-over study we compared the efficacy and safety of the new compound atorvastatin for reducing LDL-cholesterol with simvastatin or pravastatin. **METHODS:** Following a 4-week placebo-controlled baseline period patients with LDL-cholesterol between 4.1 and 6.2 mmol/l and serum triglycerides below 3.4 mmol/l were randomly assigned to treatment either with 5 or 20 mg atorvastatin, or with 10 mg simvastatin or 20 mg pravastatin once daily for 4 weeks. After a placebo-washout period of 4-6 weeks, patients switched to the alternate treatment. At the end of weeks 3 and 4 of each study phase the serum concentrations of lipid parameters and apolipoproteins as well as safety parameters were determined. **RESULTS:** A total of 78 subjects entered the study. Treatment with 5 mg atorvastatin reduced total and LDL-cholesterol by 21 and 27%, respectively, which was similar to 10 mg simvastatin (total cholesterol -20%, LDL-cholesterol -28%) and 20 mg pravastatin (-18 and -24%, respectively). The effects of this low dose of atorvastatin on triglyceride levels (-16%) was not different from that of simvastatin and pravastatin (-8 and -11%, respectively). Treatment with 20 mg atorvastatin caused significantly larger reductions in total cholesterol (-33%) and LDL-cholesterol (-44%), serum triglycerides (-23%), and apo B (-40%) compared to simvastatin and pravastatin. Atorvastatin was well-tolerated, and no serious or medically important adverse events were observed. **CONCLUSIONS:** We conclude that atorvastatin is a safe and very efficacious cholesterol-lowering agent, which also possesses significant triglyceride-lowering properties

Making medicines safer--the need for an independent drug safety board.

Wood AJ, Stein CM, Woosley R.

*N Engl J Med*. 1998 Dec 17; 339(25):1851-4.

Is academic medicine for sale?

Young SA.

*N Engl J Med.* 2000 Aug 17; 343(7):508-9.

Caution: that dose may be too high.

Zuger A.

*New York Times.* 2004.Sep.17

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