

- 1: [Pharmacoepidemiol Drug Saf.](#) 2007 Nov 15 [Epub ahead of print]

[Related Articles](#), [Links](#)



## **The patterns of antihypertensive drug prescription by cardiologists in Kerman province of Iran, 2006.**

[Sepehri G.](#), [Talebizadeh N.](#), [Mirzazadeh A.](#), [Mohsenbeigi M.](#)

Physiology Research Center, Neuroscience Research Center, University of Medical Sciences, Kerman, Iran.

**PURPOSE:** This study was performed to evaluate the antihypertensive prescribing pattern by cardiologists in outpatients attending private clinics in Kerman province, Iran during 1 year period, 2006. **METHODS:** Using random sampling method, 1102 prescriptions issued by cardiologists were investigated. The prescriptions of outpatients which contain at least one antihypertensive medication were separated for further analysis. Using World Health Organization (WHO) standard drug indicators, we evaluate the quality and quantity of prescriptions. The indices were compared between different sex groups by SPSS 11.5 software. **RESULTS:** About 39% of the patients were male. The average age of the individuals was 57.3 +/- 13. The mean number of drugs per prescription was 2.84 +/- 0.7, but the average of antihypertensive drugs per prescription was 1.4 +/- 0.3, similarly in both sexes. The most prescribed drug class was beta-blockers (46.2%) followed by calcium channel blockers (CCBs) (19.2%), angiotensin-converting enzyme (ACE) inhibitors (13.7%), diuretics (10.3%), angiotensin receptor blockers (ARBs) (9.2%) and other antihypertensive agents (1.5%). Most of the hypertensive patients (69.6%) were treated with a single drug while 31.4% of the patients received more than one drug. There was not a significant gender difference between the types of drug class used. Statins and acetyl salicylic acid (ASA) were prescribed as cardiovascular disease preventive drugs in 10.2 and 38% of hypertensive patients, respectively. **CONCLUSION:** The mean numbers of drugs per prescription by cardiologists in Kerman province of Iran were not in agreement with WHO standard drug use indicators. Lower using rate of diuretics, statins and ASA need a comprehensive reassessment of the medical management of hypertensive patients. Copyright (c) 2007 John Wiley & Sons, Ltd.

PMID: 18001003 [PubMed - as supplied by publisher]

- 
- 2: [Pharmacoepidemiol Drug Saf.](#) 2007 Nov 15 [Epub ahead of print]

[Related Articles](#), [Links](#)



## **Self-rated health as predictor of medicine use in adolescence.**

[Holstein BE.](#), [Hansen EH.](#), [Andersen A.](#), [Due P.](#)

Institute of Public Health, University of Copenhagen, Copenhagen, Denmark.

**PURPOSE:** To examine the association between self-rated health (SRH) and medicine use for four common complaints: headache, stomach-ache, difficulties in getting to sleep and nervousness, in a nationally representative sample of adolescents. **METHODS:** The study population comprised of all students in the fifth, seventh and ninth grade (mean ages 11.6, 13.6 and 15.6 years) in a random sample of schools in Denmark 2002, participation rate 90.6%, n = 4.824. The students reported health problems, medicine use, social and psychosocial conditions in an anonymous and standardized questionnaire. The outcome measure was self-reported medicine use during the past month and the determinant was SRH measured by one item. **RESULTS:** There was an association between poor/fair SRH and medicine use for headache and stomach-ache. The associations remained statistically significant even after adjustment for frequency of the complaint for which the medicine was used: OR (95%CI) for medicine use for headache was 1.54 (1.10-2.14) among boys with poor/fair SRH and 1.50 (1.12-2.03) among girls with

poor/fair SRH. A similar association was found between poor SRH and medicine use for stomach-ache for both boys (OR = 3.41 (2.09-5.55)) and girls (OR = 1.90 (1.36-2.67)). Further, there was an association between poor/fair SRH and medicine use for difficulties in getting to sleep among girls, OR = 2.66 (1.26-5.63) but not among boys. There was no association between SRH and medicine use for nervousness. CONCLUSION: Poor/fair SRH is associated with medicine use for aches among Danish adolescents. Copyright (c) 2007 John Wiley & Sons, Ltd.

PMID: 18001005 [PubMed - as supplied by publisher]

---

□ 3: [BioDrugs](#). 1998 Dec;10(6):437-45.

[Related Articles](#), [Links](#)

### **Cyclosporin in rheumatoid arthritis: monitoring for adverse effects and clinically significant drug interactions.**

[Dijkmans B](#), [Gerards A](#).

Department of Rheumatology, Academic Hospital Free University Amsterdam, Amsterdam, The Netherlands.

While cyclosporin has an established role in the treatment of rheumatoid arthritis there is concern about adverse effects, mainly related to renal function. With new interest being generated in cyclosporin combination therapy, and the availability of a new form of cyclosporin (cyclosporin microemulsion), focus on adverse effects and drug interactions of this compound remains important. Over the years, rheumatologists have been aware of these adverse effects and consensus meetings have resulted in guidelines for the use of cyclosporin. If these guidelines are followed, structural renal damage can be minimal. Cyclosporin should be started at a low dose and titrated against the highest acceptable increase in serum creatinine, that is, a 30% increase over the pretreatment value. At present, there is no evidence that cyclosporin in combination with other antirheumatics leads to increased toxicity. With regard to long term unwanted effects, neither the pattern nor the risk of malignancies associated with the use of cyclosporin seems to differ from other antirheumatics. The place of cyclosporin in the treatment of rheumatoid arthritis seems to be established. The most promising results will come from early rheumatoid arthritis combination studies involving cyclosporin with other antirheumatics, especially methotrexate.

PMID: 18020613 [PubMed - in process]

---

□ 4: [J Clin Pharm Ther](#). 2007 Dec;32(6):585-93.

[Related Articles](#), [Links](#)



### **Pharmacokinetic interaction between ketoconazole and praziquantel in healthy volunteers.**

[Ridtitid W](#), [Ratsamemonthon K](#), [Mahatthanatrakul W](#), [Wongnawa M](#).

Clinical Pharmacology Laboratory, Department of Pharmacology, Faculty of Science, Prince of Songkla University, Hat Yai, Songkhla, Thailand.

Background: Praziquantel, a broad-spectrum anthelmintic, has been reported to undergo extensive first-pass metabolism by cytochrome P450 (CYP) enzymes in vivo. Ketoconazole, a potent CYP3A4 inhibitor, is known to markedly increase plasma concentrations of many co-administered drugs. However, no data are available on the potential pharmacokinetic drug interaction between ketoconazole and praziquantel in humans. Objective: To investigate the potential pharmacokinetic interaction of ketoconazole with praziquantel in healthy adult Thai male volunteers. Methods: In an open-label, randomized two-phase crossover study, separated by a 2-week period, 10 healthy adult Thai male volunteers ingested a single dose of 20 mg/kg praziquantel alone or with co-administration of 400-mg

ketoconazole orally daily for 5 days. Venous blood samples were collected at specific times for a 24-h period. Plasma concentrations of praziquantel were determined using high-performance liquid chromatography. A non-compartmental model was applied for pharmacokinetic parameter analysis of praziquantel. Results: Concurrent administration of ketoconazole with praziquantel significantly increased the mean area under the curve from time zero to infinity (AUC(0-alpha)) and maximum plasma concentration (C(max)) of praziquantel by 93% (955.94 +/- 307.74 vs. 1843.10 +/- 336.39 ng h/mL; P < 0.01) and 102% (183.38 +/- 43.90 vs. 371.31 +/- 44.63 ng/mL; P < 0.01), respectively, whereas the mean total clearance (Cl/F) of praziquantel was significantly decreased by 58% (2.65 +/- 0.64 vs. 1.11 +/- 0.35 mL/h/kg; P < 0.01). Conclusion: Ketoconazole co-administration alters the pharmacokinetics of praziquantel in humans, possibly through inhibition of CYP3A, particularly CYP3A4, first-pass metabolism of praziquantel. Our data suggest that when praziquantel is co-administered with ketoconazole, the dose of praziquantel could be reduced to half the standard dose of praziquantel to reduce the cost of therapy.

PMID: 18021336 [PubMed - in process]

---

□ 5: [Lancet](#). 2007 Nov 17;370(9600):1706-13.

[Related Articles](#), [Links](#)



### **Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials.**

[Christensen R](#), [Kristensen PK](#), [Bartels EM](#), [Bliddal H](#), [Astrup A](#).

The Parker Institute, Musculoskeletal Statistics Unit, Frederiksberg Hospital, Frederiksberg, Denmark.

**BACKGROUND:** Since the prevalence of obesity continues to increase, there is a demand for effective and safe anti-obesity agents that can produce and maintain weight loss and improve comorbidity. We did a meta-analysis of all published randomised controlled trials to assess the efficacy and safety of the newly approved anti-obesity agent rimonabant. **METHODS:** We searched The Cochrane database and Controlled Trials Register, Medline via Pubmed, Embase via WebSpirs, Web of Science, Scopus, and reference lists up to July, 2007. We collected data from four double-blind, randomised controlled trials (including 4105 participants) that compared 20 mg per day rimonabant with placebo. **FINDINGS:** Patients given rimonabant had a 4.7 kg (95% CI 4.1-5.3 kg; p<0.0001) greater weight reduction after 1 year than did those given placebo. Rimonabant caused significantly more adverse events than did placebo (OR=1.4; p=0.0007; number needed to harm=25 individuals [95% CI 17-58]), and 1.4 times more serious adverse events (OR=1.4; p=0.03; number needed to harm=59 [27-830]). Patients given rimonabant were 2.5 times more likely to discontinue the treatment because of depressive mood disorders than were those given placebo (OR=2.5; p=0.01; number needed to harm=49 [19-316]). Furthermore, anxiety caused more patients to discontinue treatment in rimonabant groups than in placebo groups (OR=3.0; p=0.03; number needed to harm=166 [47-3716]). **INTERPRETATION:** Our findings suggest that 20 mg per day rimonabant increases the risk of psychiatric adverse events--ie, depressed mood disorders and anxiety--despite depressed mood being an exclusion criterion in these trials. Taken together with the recent US Food and Drug Administration finding of increased risk of suicide during treatment with rimonabant, we recommend increased alertness by physicians to these potentially severe psychiatric adverse reactions.

Publication Types:

- [Research Support, Non-U.S. Gov't](#)

PMID: 18022033 [PubMed - in process]

---

□ 6: [Radiology](#). 2007 Dec;245(3):919-21.

[Related Articles](#), [Links](#)

## Management of Patients with History of Adverse Effects to Contrast Media When Pulmonary Artery CT Angiography Is Required.

[Bierry G](#), [Kellner F](#), [Barnig C](#), [Woodard PK](#), [Goodman LR](#), [Weg JG](#), [Stein PD](#).

Department of Radiology, University Hospital of Strasbourg, 1 Place de l'Hôpital, 67091 Strasbourg Cedex, France [guillaume.bierry@chru-strasbourg.fr](mailto:guillaume.bierry@chru-strasbourg.fr).

PMID: 18024463 [PubMed - in process]

---

7: [CMAJ](#). 2007 Nov 20;177(11):1369-70.

[Related Articles](#), [Links](#)

Free full text article at  
[www.cmaj.ca](http://www.cmaj.ca)

**FREE** full text article  
in PubMed Central

## The effect of publication on Internet-based solicitation of personal-injury litigants.

[Juurlink DN](#), [Park-Wyllie LY](#), [Kapral MK](#).

Serious adverse drug events can prompt personal-injury lawsuits. However, the extent to which biomedical publication regarding drug-induced harm can influence the legal process has not been well characterized. Using an advanced Google search strategy, we determined the number of Internet "hits" for websites soliciting plaintiffs for medicolegal action before and after publication of a study that highlighted the risk of dysglycemia among patients taking the antibiotic gatifloxacin. We found that early online release and print publication were associated with an immediate and sustained increase in the number of websites soliciting plaintiffs for legal action.

Publication Types:

- [Letter](#)

PMID: 18025428 [PubMed - in process]

---

8: [Ann Intern Med](#). 2007 Nov 19 [Epub ahead of print]

[Related Articles](#), [Links](#)

 Full Text  
Ann Intern Med

## Systematic Review: Comparative Effectiveness and Harms of Disease-Modifying Medications for Rheumatoid Arthritis.

[Donahue KE](#), [Gartlehner G](#), [Jonas DE](#), [Lux LJ](#), [Thieda P](#), [Jonas BL](#), [Hansen RA](#), [Morgan LC](#), [Lohr KN](#).

the University of North Carolina and Cecil G Sheps Center for Health Services Research, Chapel Hill, North Carolina; RTI International, Research Triangle Park, North Carolina; Danube University, Krems, Austria; and Ludwig Boltzmann Institute for Health Technology Assessments, Vienna, Austria.

**BACKGROUND:** The comparative effectiveness of rheumatoid arthritis therapies is uncertain.

**PURPOSE:** To compare the benefits and harms of disease-modifying antirheumatic drugs (DMARDs) for adults with rheumatoid arthritis. **DATA SOURCES:** We searched records limited to the English language and to studies of adults by using MEDLINE, EMBASE, The Cochrane Library, and International Pharmaceutical Abstracts from 1980 to September 2007. **STUDY SELECTION:** Two persons independently selected relevant head-to-head trials and prospective cohort studies with at least 100 participants and 12-week follow-up and relevant good- or fair-quality meta-analyses that compared benefits or harms of 11 drug therapies. For harms, they included retrospective cohort studies. **DATA**

EXTRACTION: Study design, interventions, outcomes, and quality were extracted according to a standard protocol. DATA SYNTHESIS: Head-to-head trials (n = 23) showed no clinically important differences in efficacy among synthetic DMARDs (limited to methotrexate, leflunomide, and sulfasalazine) or among anti-tumor necrosis factor drugs (adalimumab, etanercept, and infliximab). Monotherapy with anti-tumor necrosis factor drugs resulted in better radiographic outcomes than did methotrexate but no important differences in clinical outcomes (for example, 20%, 50%, or 70% improvement according to American College of Rheumatology response criteria). Various combinations of biological DMARDs plus methotrexate improved clinical response rates and functional outcomes more than monotherapy with either methotrexate or biological DMARDs. In patients whose monotherapy failed, combination with synthetic DMARDs improved response rates. Numbers and types of short-term adverse events were similar for biological and synthetic DMARDs. The evidence was insufficient to draw conclusions about differences for rare but serious adverse events for biological DMARDs. Limitations: Most studies were short-term efficacy trials conducted in selected populations with few comorbid conditions. CONCLUSION: Limited available comparative evidence does not support one monotherapy over another for adults with rheumatoid arthritis. Although combination therapy is more effective for patients whose monotherapy fails, the evidence is insufficient to draw firm conclusions about whether one combination or treatment strategy is better than another or is the best treatment for early rheumatoid arthritis.

PMID: 18025440 [PubMed - as supplied by publisher]

---

□ 9: [J Clin Pharmacol](#). 2007 Nov 19 [Epub ahead of print]

[Related Articles](#), [Links](#)



### **Pharmacokinetic Interaction Between Voriconazole and Efavirenz at Steady State in Healthy Male Subjects.**

[Liu P](#), [Foster G](#), [Labadie RR](#), [Gutierrez MJ](#), [Sharma A](#).

Pfizer Global Research and Development.

A randomized, placebo-controlled (with respect to voriconazole), 2-period, multiple-dose intragroup fixed-dose sequence study was conducted in 34 healthy male subjects to evaluate the interactions between voriconazole (triazole antifungal agent) and efavirenz (reverse transcriptase inhibitor). In period 1, subjects received 200 mg twice-daily (bid) voriconazole (n = 17) or placebo (n = 17) for 3 days (400-mg bid loading doses on day 1). In period 2, following a 7-day washout, subjects received 400 mg once-daily (qd) efavirenz alone for 10 days (days 11-20). Then efavirenz was coadministered with 200 mg bid voriconazole or placebo for the next 9 days (days 21-29). Serial plasma voriconazole and efavirenz concentrations were measured on days 3, 19, and 29, and the safety data were collected throughout the study. The 400-mg qd efavirenz dose substantially reduced the steady-state mean voriconazole area under the curve over the dosing interval (AUC<sub>0-12</sub>) by 80% (90% confidence interval [CI], 75%-84%) and peak concentration (C<sub>max</sub>) by 66% (90% CI, 57%-73%). The decrease in voriconazole exposure during coadministration is probably mainly due to the induction of CYP2C19 and CYP2C9 by efavirenz. The 200 mg bid voriconazole increased the steady-state mean AUC<sub>0-24</sub> and C<sub>max</sub> of efavirenz by 43% (90% CI, 36%-51%) and 37% (90% CI, 29%-46%), respectively. The increase in efavirenz exposure during coadministration is probably due to the inhibition of CYP3A4 by voriconazole. Coadministration of 200 mg bid voriconazole with 400 mg (or higher) qd efavirenz is contraindicated due to the clinically significant effect of efavirenz on voriconazole pharmacokinetics.

PMID: 18025525 [PubMed - as supplied by publisher]

---

□ 10: [Ann Pharmacother](#). 2007 Nov 20 [Epub ahead of print]

[Related Articles](#), [Links](#)

### **Risk Factors for Self-Reported Adverse Drug Events Among Medicare Enrollees (January).**

Department of Pharmaceutical Socioeconomics, College of Pharmacy, University of Iowa, Iowa City, IA.

**BACKGROUND:** Adverse drug events (ADEs) occur in older adults. ADEs occur in up to 6.5% of all hospitalized patients and outpatients, and about 28% of these events are preventable. The proportion of outpatients with an ADE ranges from 5% to 35%, depending on the exact definition used. There is a critical need to examine the risk factors associated with having an ADE to increase awareness about medication safety among older adults. **OBJECTIVE:** To quantify the association between risk factors such as the number of pharmacies used by patients and their concern and necessity beliefs about medicines, and self-reported ADEs. **METHODS:** A cross-sectional Internet survey was administered by Harris Interactive. Harris Interactive asked individuals from their online panel who were 65 years of age or older, US residents, and enrolled in Medicare to complete the survey. A convenience sample of 1220 anonymous surveys was obtained. Multiple logistic regression analysis was performed. The dependent variable was self-reported ADEs, defined as the patient's visiting a physician to report an unwanted reaction or medicine problem in the past year. Independent variables included sociodemographics, self-rated health, number of medications, sum of symptoms experienced, concern and necessity beliefs about medicines, number of pharmacies, and whether subjects skipped doses of their medications to save money or stopped taking the drugs due to cost. **RESULTS:** Eighteen percent of respondents reported an ADE. ADEs were related to being female (OR 1.56; 95% CI 1.05 to 2.33), number of pharmacies (OR 3.40; 95% CI 1.56 to 7.41), number of symptoms experienced (OR 3.39; 95% CI 1.87 to 6.14), concern beliefs about medicines (OR 1.14; 95% CI 1.08 to 1.20), and having a graduate academic degree (OR 2.17; 95% CI 1.41 to 3.36). **CONCLUSIONS:** The number of pharmacies, concern beliefs about medicines, and number of symptoms experienced in the past month were associated with self-reported ADEs. Discussing patients' beliefs about their drug therapy with them is likely to affect their expectations and interpretation of symptoms, as well as future attributions regarding drug therapy.

PMID: 18029427 [PubMed - as supplied by publisher]

---

□ **11:** [BioDrugs](#). 1999 Mar;11(3):185-200.

[Related Articles](#), [Links](#)

## **Treatment of drug-induced agranulocytosis with haematopoietic growth factors: a review of the clinical experience.**

[Vial T](#), [Gallant C](#), [Choqu-Kastylevsky G](#), [Descotes J](#).

Centre Anti-Poison, Centre de Pharmacovigilance, Lyon, France.

Although drug-induced agranulocytosis is infrequent, it is of concern as the mortality rate ranges from 6 to 10%. Since the approval of granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), these drugs have been increasingly used in the management of drug-induced agranulocytosis. Unfortunately, most of the data regarding the use of these agents in patients with drug-induced agranulocytosis comes from case reports. In light of the low incidence of drug-induced agranulocytosis, the large variety of offending drugs with potentially different toxic mechanisms and the wide range of neutropenia duration among patients with agranulocytosis, randomised, double-blind studies are unlikely to be performed. Case reports provide promising results with a shortening in the duration of agranulocytosis, a possible reduction in the duration of hospitalisation and the fatality rate in patients treated with haematopoietic growth factors (HGF) compared with historical controls. A therapeutic effect is also suggested by reports of reductions in the neutrophil count after HGF discontinuation following an initial increase. The results of recent case series are less positive, with only a moderate, but usually not significant, reduction in the duration of neutropenia in patients treated with HGF, as compared with those receiving routine care. A Japanese study indicated that G-CSF was effective in patients with mild-to-moderate antithyroid drug-induced neutropenia, whereas no clear benefit was apparent in those with severe neutropenia. Several factors, for

example, early recognition and improved management of individual cases with better supportive care, have contributed to a decrease in the overall mortality of drug-induced agranulocytosis. HGF are expected to further reduce mortality. Guidelines for the use of HGF in patients with febrile neutropenia, as established by the American Society of Clinical Oncology, are probably valuable for the management of drug-induced agranulocytosis. In accordance with these recommendations, the use of HGF may be recommended in patients with severe neutropenia and/or poor prognostic factors. Whether the absence of myeloid precursors or presence of promyelocytes or myelocytes in bone marrow examination represents optimal conditions for HGF treatment is still unknown. Most authors agree that treatment should be administered early in the course of the disease. An interesting approach, in which treatment decisions are based on the granulocyte count 4 hours after a single dose of G-CSF in patients with antithyroid drug-associated neutropenia should be more extensively evaluated.

PMID: 18031129 [PubMed - in process]

---

□ **12:** [BioDrugs](#). 1999 Apr;11(4):229-37.

[Related Articles](#), [Links](#)

### **Managing the neuropsychiatric adverse effects of interferon treatment.**

[Valentine AD](#).

Department of Neuro-Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA.

Patients who receive interferons are vulnerable to a wide variety of neuropsychiatric adverse effects which can seriously compromise otherwise effective therapy. The nature and severity of the adverse effects are, in part, dose dependent, though there is significant variability. Effective treatment of interferon adverse effects is hindered by the absence of an identified mechanism of toxicity and lack of controlled intervention trials. Successful management of adverse effects is facilitated by a multimodal approach, starting with pre-treatment screening and discussion. Behavioural techniques help maintain daily function. Dose reduction or drug holidays may be required. Pharmacological treatment is based largely on clinical experience, though formal studies are underway. Familiarity with several classes of psychotropic medications is required, including antidepressants, anxiolytics, antipsychotics and psychostimulants. Together, these interventions may be used to reduce severity of interferon behavioural adverse effects to tolerable levels.

PMID: 18031133 [PubMed - in process]

---

□ **13:** [BioDrugs](#). 2000 Nov;14(5):299-318.

[Related Articles](#), [Links](#)

### **Interleukin-2 in cancer therapy: uses and optimum management of adverse effects.**

[Mekhail T](#), [Wood L](#), [Bukowski R](#).

Experimental Therapeutic Program, Taussig Cancer Center, The Cleveland Clinic Foundation, Cleveland, Ohio, USA.

Recombinant interleukin-2 (rIL-2) produces remissions in several human tumours, including metastatic renal cell cancer (RCC) and malignant melanoma. High-dose intravenous bolus rIL-2 is approved in the US in these 2 indications, based on evidence of rIL-2-induced durable remissions in a significant minority of patients. Due to the toxicity associated with high-dose rIL-2, alternative regimens were investigated in RCC, including low-dose intravenous bolus, subcutaneous outpatient regimens and continuous intravenous infusion, yielding similar response rates. A prospective randomised trial comparing different doses and routes of administration is underway. Because response rates to single agent rIL-2 are inadequate, combination therapies were studied. In RCC patients, a combination of rIL-2 and IFNalpha resulted in better response rates than either cytokine alone, with no apparent survival

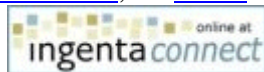
advantage. Combination with chemotherapy increased toxicity and had no proven benefit. Results of adoptive immunotherapy studies combining rIL-2 with either lymphokine-activated killer cells or tumour infiltrating lymphocytes were comparable to those of rIL-2 alone. In malignant melanoma, combination therapy of rIL-2 with chemotherapy was explored. Results of single-institution phase II combination studies of variable chemotherapy and rIL-2 and IFNalpha regimens were promising and randomised trials are underway. rIL-2 is being evaluated in haematological malignancies. The rationale is based on pre-clinical evidence that a variety of leukaemic blasts are sensitive to cytolysis or growth inhibition mediated by rIL-2-activated immune effector cells. New immunotherapeutic strategies may ultimately improve the anti-tumour efficacy of rIL-2-based therapy. Early trials using rIL-2 as adjuvant therapy to vaccines or dendritic cell-based therapy have yielded promising results. rIL-2 therapy initiates a cytokine-mediated pro-inflammatory process leading to an adverse effect profile that is quite different from traditional chemotherapeutic agents. Dose-limiting toxicities are primarily cardiovascular and pulmonary and are dose-dependent in frequency and severity. Patients receiving high-dose regimens may require intensive care unit support, limiting its use to those with excellent performance status and adequate organ function. Patients receiving less intensive dose regimens may require less rigorous screening and monitoring. It has been postulated that rIL-2 related toxicity is mediated through the release of secondary cytokines, including TNF, IFNgamma, IL-6 and IL-1. With the increasing understanding of the pathophysiological mechanisms of the effects of rIL-2, it is possible that concurrent administration of selective cytokine antagonists may reduce the toxicity associated with rIL-2 without interfering with its anti-neoplastic activity.

PMID: 18034575 [PubMed - in process]

---

□ **14:** [Allergy Asthma Proc.](#) 2007 Sep-Oct;28(5):517-24.

[Related Articles](#), [Links](#)



### **New concepts in the management of adverse drug reactions.**

[Bahna SL](#), [Khalili B](#).

Allergy and Immunology Section, Louisiana State University Health Sciences Center, Shreveport, LA 71139-3932, USA. sbahna@lsuhsc.edu

Our understanding of drug reactions and their management has changed markedly in recent years with the development of several new concepts. Epidermal cell death seen in Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) may result from Fas-Fas ligand-mediated apoptosis. Intravenous immunoglobulin (IVIG) contains anti-Fas antibodies that can abrogate apoptosis. Most studies on IVIG in SJS and TEN reported improvement in arresting disease progression and reduction in time to healing. Furthermore, several studies have dispelled the myth of sulfonamide cross-reactivity. Immune-mediated reactions against antibacterial sulfonamides are directed against two unique side chains that non-antibacterial sulfonamides do not contain. Certain patients seem to have a genetic predisposition for "multiple drug sensitivities." Hence, they may react to several drugs that are not necessarily cross-reacting. Also, multiple studies have shown that IgE-mediated nonsteroidal anti-inflammatory drugs (NSAIDs) cross-reactivity is uncommon. Rather, it is cyclooxygenase (COX) 1 inhibition that results in pseudoallergic reactions to multiple NSAIDs. Several studies have indicated that selective COX-2 inhibitors can be safely administered in patients with aspirin-exacerbated respiratory disease and NSAID-induced cutaneous reactions, although their use has been curtailed by their cardiovascular side effects. Biological agents, such as infliximab, are being increasingly used for a variety of diseases and have caused adverse reactions in some patients. Studies differ as to whether concomitant immunosuppressive use with infliximab affects the development of drug-specific antibodies and infusion reactions. Successful desensitization protocols have been developed for reactions to some of these agents.

PMID: 18034968 [PubMed - in process]

---

□ **15:** [Am Heart J.](#) 2007 Dec;154(6):1206-20. Epub 2007 Sep 14.

## **A framework for quality improvement: an analysis of factors responsible for improvement at hospitals participating in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) quality improvement initiative.**

[Glickman SW](#), [Boulding W](#), [Staelin R](#), [Mulgund J](#), [Roe MT](#), [Lytle BL](#), [Rumsfeld JS](#), [Gibler WB](#), [Ohman EM](#), [Schulman KA](#), [Peterson ED](#).

Center for Clinical and Genetic Economics, Duke University Medical Center, Durham, NC, USA.

**BACKGROUND:** Hospitals are under increasing pressure to improve their quality of care. However, a key question remains: how can hospitals best design and implement successful quality improvement (QI) programs? Hospitals currently employ a variety of QI initiatives but have little empirical evidence on which to base their quality efforts. **METHODS:** We designed and applied a hospital cross-sectional survey to 212 hospitals participating in CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines), a voluntary QI initiative of patients with non-ST-segment elevation acute coronary syndromes (NSTEMI ACS). We factor analysis and an ordinary least squares regression model to determine the key hospital factors most associated with unexpected improvements in institutional QI in the treatment of NSTEMI ACS. **RESULTS:** From 2002 to 2004, the following factors had a significant association with unexpected increases in the 2004 QI in NSTEMI ACS treatment: the use of CRUSADE QI tools, clinical commitment to quality by a cardiology coadvocate, institutional financial commitment to quality, and barriers to QI related to resource availability and cultural resistance to change (all  $P < .10$ ). Of these factors, optimal use of CRUSADE QI tools was associated with the highest absolute improvement in process adherence score relative to other factors. **CONCLUSIONS:** We identified several institutional factors associated with improved quality of care in the treatment of high-risk NSTEMI ACS. We hope that this evidence-based framework will help guide the development and implementation of future QI programs in order to improve the institutional quality of care for NSTEMI ACS.

PMID: 18035096 [PubMed - in process]

---

□ 16: [Lepr Rev.](#) 2007 Sep;78(3):197-215.

[Related Articles](#), [Links](#)

## **The role of thalidomide in the management of erythema nodosum leprosum.**

[Walker SL](#), [Waters MF](#), [Lockwood DN](#).

Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel St, London, UK. drstevewalker@hotmail.com

Erythema nodosum leprosum (ENL, Type 2 reactions) complicates lepromatous and borderline lepromatous leprosy and can affect many organ systems, often with irreversible damage. The reactions commonly occur in the 2 years after starting treatment and often run a recurrent or chronic course, sometimes for many years. Even with WHO multi-drug therapy about 30% of LL patients experience ENL. We review drug management of ENL focussing on data from controlled trials and other studies. The treatment of ENL is difficult because high doses of steroids may be required for prolonged periods and do not always control the inflammation. The paradox of ENL is that it can be a life-threatening disorder and requires control with immunosuppression which may itself pose life-threatening risks for patients. Treatment with thalidomide provides an effective alternative to steroid therapy, gives better long-term control and avoids the adverse effects of prolonged steroid therapy. Controlled clinical trials have demonstrated that thalidomide rapidly controls ENL and is superior to aspirin and pentoxifylline. However, thalidomide is teratogenic when taken in early pregnancy and is unavailable in many leprosy endemic countries. We discuss the role of thalidomide in treating ENL, the complications encountered

and risk reduction strategies that can be used. These include good patient selection and counselling, close supervision and adequate access to appropriate contraception. Further research is needed to improve the understanding and treatment of this severe and debilitating complication of leprosy. Topics for research include: i. The development of validated tools to measure the severity and/or activity of ENL. ii. A detailed assessment of the neurotoxic effects of thalidomide when used to treat ENL. iii. A well designed trial comparing thalidomide with prednisolone. iv. The development of a safe and effective alternative to both steroids and thalidomide.

Publication Types:

- [Research Support, Non-U.S. Gov't](#)

PMID: 18035771 [PubMed - in process]

---

- 17:** [Drug Saf.](#) 2007;30(12):1083-5.

[Links](#)

**[In Process Citation]**

[No authors listed]

PMID: 18035861 [PubMed - in process]

---

- 18:** [Drug Saf.](#) 2007;30(12):1087-92.

[Related Articles](#), [Links](#)

**Biotherapeutics in the Era of Biosimilars : What Really Matters is Patient Safety.**

[Declerck PJ.](#)

Laboratory for Pharmaceutical Biology, Faculty of Pharmaceutical Sciences, Katholieke Universiteit Leuven, Leuven, Belgium.

PMID: 18035862 [PubMed - in process]

---

- 19:** [Drug Saf.](#) 2007;30(12):1093-110.

[Related Articles](#), [Links](#)

**Cardiac Repolarisation and Drug Regulation : Assessing Cardiac Safety 10 Years after the CPMP Guidance.**

[Shah RR.](#)

Rashmi Shah Consultancy Ltd, Gerrards Cross, Buckinghamshire, UK.

December 2007 marks the 10-year anniversary of the first regulatory guidance for evaluation of drug-induced QT interval prolongation. A decade on, it seems surprising that this document, which was released by the Committee on Proprietary Medicinal Products, caused such acrimony in the industry. Sponsors now routinely evaluate their new drugs for an effect on cardiac electrophysiology in preclinical studies, in addition to obtaining ECGs in all phases of drug development and conducting a formal thorough QT study in humans. However, concurrently, new concerns have also emerged on broader issues related to the cardiovascular safety of drugs because of their potential to shorten the QT interval as well as to induce proischaemic, profibrotic or prothrombotic effects. Drugs may also have an indirect effect by adversely affecting one or more of the cardiovascular risk factors (e.g. through fluid retention or induction of dyslipidaemia). In addition to peroxisome proliferator-activated receptor

agonists and cyclo-oxygenase 2 selective inhibitors, three other drugs, darbepoetin alfa, pergolide and tegaserod, provide a more contemporary regulatory stance on tolerance of cardiovascular risk of drugs and their benefit-risk assessment. This recent, more assertive, risk-averse stance has significant implications for future drug development. These include the routine evaluation of cardiovascular safety for certain classes of drugs. Drugs that are intended for long-term use will almost certainly require long-term clinical evaluation in studies that enrol populations that most closely resemble the ultimate target population. Novel mechanisms of action and biomarkers by themselves are no guarantee of improved safety or benefits. Even some traditional biomarkers have come to be viewed with scepticism. Requirements for more extensive and earlier postmarketing assessment of clinical benefits and rare, but serious risks associated with new medicinal products should create a new standard of evidence for industry and regulators and almost certainly result in better assessment of benefit/risk, more effective and balanced regulatory actions and better care for patients.

PMID: 18035863 [PubMed - in process]

---

□ 20: [Drug Saf.](#) 2007;30(12):1111-1125.

[Related Articles](#), [Links](#)

### **Interventions to Reduce Dosing Errors in Children : A Systematic Review of the Literature.**

[Conroy S](#), [Sweis D](#), [Planner C](#), [Yeung V](#), [Collier J](#), [Haines L](#), [Wong IC](#).

Academic Division of Child Health, Derbyshire Children's Hospital, University of Nottingham, Nottingham, UK.

Children are a particularly challenging group of patients when trying to ensure the safe use of medicines. The increased need for calculations, dilutions and manipulations of paediatric medicines, together with a need to dose on an individual patient basis using age, gestational age, weight and surface area, means that they are more prone to medication errors at each stage of the medicines management process. It is already known that dose calculation errors are the most common type of medication error in neonatal and paediatric patients. Interventions to reduce the risk of dose calculation errors are therefore urgently needed. A systematic literature review was conducted to identify published articles reporting interventions; 28 studies were found to be relevant. The main interventions found were computerised physician order entry (CPOE) and computer-aided prescribing. Most CPOE and computer-aided prescribing studies showed some degree of reduction in medication errors, with some claiming no errors occurring after implementation of the intervention. However, one study showed a significant increase in mortality after the implementation of CPOE. Further research is needed to investigate outcomes such as mortality and economics. Unit dose dispensing systems and educational/risk management programmes were also shown to reduce medication errors in children. Although it is suggested that 'smart' intravenous pumps can potentially reduce infusion errors in children, there is insufficient information to draw a conclusion because of a lack of research. Most interventions identified were US based, and since medicine management processes are currently different in different countries, there is a need to interpret the information carefully when considering implementing interventions elsewhere.

PMID: 18035864 [PubMed - as supplied by publisher]

---

□ 21: [Drug Saf.](#) 2007;30(12):1127-42.

[Related Articles](#), [Links](#)

### **Bodyweight changes associated with antihyperglycaemic agents in type 2 diabetes mellitus.**

[Hermansen K](#), [Mortensen LS](#).

Aarhus University Hospital, Aarhus, Denmark.

The majority of patients with type 2 diabetes mellitus are overweight or obese at the time of diagnosis, and obesity is a recognised risk factor for type 2 diabetes and coronary heart disease (CHD). Conversely, weight loss has been shown to improve glycaemic control in patients with type 2 diabetes, as well as to lower the risk of CHD. The traditional pharmacotherapies for type 2 diabetes can further increase weight and this may undermine the benefits of improved glycaemic control. Furthermore, patients' desire to avoid weight gain may jeopardise compliance with treatment, thereby limiting treatment success and indirectly increasing the risk of long-term complications. This review evaluates the influences of established and emerging therapies on bodyweight in type 2 diabetes. Improvement in glycaemic control with insulin secretagogues has been associated with weight gain. On the other hand, biguanides such as metformin have been consistently shown to have a beneficial effect on weight; metformin appears to modestly reduce weight when used as a monotherapy. alpha-Glucosidase inhibitors are considered weight neutral; in fact, the results of some studies show that they cause reductions in weight. Thiazolidinediones (TZDs) are typically associated with weight gain and increased risk of oedema, while the impact of some TZDs, such as pioglitazone, on lipid homeostasis could be beneficial. Insulin, the most effective therapy when oral agents are ineffective, has always been linked to significant weight gain. Newly developed insulin analogues can lower the risk of hypoglycaemia compared with human insulin, but most have no advantage in terms of weight gain. The basal analogue insulin detemir, however, has been demonstrated to cause weight gain to a lesser extent than human insulin. The emerging treatments, such as glucagon-like peptide-1 agonists and the amylin analogue, pramlintide, seem able to decrease weight in patients with type 2 diabetes, whereas dipeptidyl peptidase-4 inhibitors seem to be weight neutral. In summary, while reduction of hyperglycaemia remains the foremost goal in the treatment of patients with type 2 diabetes, the avoidance of weight gain may be a clinically important secondary goal. This is already possible with careful selection of available therapies, while several emerging therapies promise to further extend the options available.

PMID: 18035865 [PubMed - in process]

---

□ 22: [Drug Saf.](#) 2007;30(12):1143-1149.

[Related Articles](#), [Links](#)

## **Detection of Spironolactone-Associated Hyperkalaemia Following the Randomized Aldactone Evaluation Study (RALES).**

[Hauben M](#), [Reich L](#), [Gerrits CM](#), [Madigan D](#).

Risk Management Strategy, Pfizer Inc., New York, New York, USA  
Department of Medicine, New York University School of Medicine, New York, New York, USA  
Department of Pharmacology and Department of Community and Preventive Medicine, New York Medical College, Valhalla, New York, USA  
School of Information, Computing, and Mathematics, Brunel University, London, UK.

**INTRODUCTION:** A population-based analysis has suggested that the publication of the RALES (Randomized Aldactone Evaluation Study) in late 1999 was associated with both the wider use of spironolactone to treat heart failure and a corresponding increase in hyperkalaemia-associated morbidity and mortality in patients also being treated with ACE inhibitors. **OBJECTIVES:** To gain further insight into the reporting of spironolactone-associated hyperkalaemia in an independent dataset by analysing the spontaneous reporting experience in relation to the publication of RALES, and to determine whether the implementation of a commonly used data mining algorithm (DMA) might have directed the attention of safety reviewers to the spironolactone/hyperkalaemia association in advance of epidemiological findings. **METHODS:** We calculated the reporting rate of spironolactone-associated hyperkalaemia per 1000 reports per year from 1970 through to the end of 2005 by identifying relevant cases in the US FDA Adverse Event Reporting System. We did this for reports of spironolactone-associated hyperkalaemia (where spironolactone was listed as a suspect drug) and according to whether the reports listed an ACE inhibitor as a co-suspect or concomitant medication. A further statistical analysis of the overall reporting of spironolactone (suspect drug)-associated hyperkalaemia was also performed. We also performed 3-dimensional (3-D; drug-drug-event) disproportionality analyses using a DMA known as the multi-item gamma-Poisson shrinker, which allows the calculation and display of a

3-D disproportionality metric known as the 'interaction signal score' (INTSS). This metric is a measure of the strength of a higher order reporting relationship of a triplet (i.e. drug-drug-event) association above and beyond what would be expected from the largest disproportionalities associated with the individual 2-way associations. RESULTS: Visual inspection of a graph of the reporting frequency of spironolactone (suspect drug)-associated hyperkalaemia per 1000 reports was highly suggestive of a change point. The t-test on the arcsine-transformed data showed a significant difference in reporting of spironolactone-hyperkalaemia combination through 1999 compared with 2000 onwards ( $p < 0.001$ ). When examining the reporting time trends according to the presence or absence of an ACE inhibitor, the change point seemed to be mostly attributable to an increase in the number of spironolactone (suspect drug)-associated hyperkalaemia reports with ACE inhibitors listed as a co-suspect drug. No obvious change points in INTSSs for spironolactone-ACE inhibitor-hyperkalaemia reports were observed. DISCUSSION: Although we could not pinpoint the relative contribution of many possible artifacts in the reporting process, as well as increased drug exposure, increased adverse event incidence and/or a change in patient monitoring practices, to our findings, we observed a notable change in reporting frequency of spironolactone-associated hyperkalaemia in temporal proximity to the publication of RALES. Evidence of this was provided by a trend analysis depicted in a simple graph that was supported by statistical analysis. The observed trend was in large part due to increased reporting of spironolactone-associated hyperkalaemia with reported co-medication with ACE inhibitors. CONCLUSION: These findings are consistent with those originally reported in an epidemiological analysis. In this retrospective exercise, a simple graph was more illuminating than more complex data mining analyses.

PMID: 18035866 [PubMed - as supplied by publisher]

---

□ 23: [Drug Saf.](#) 2007;30(12):1151-60.  
[Related Articles](#), [Links](#)

## **Comparative Safety of Long-Acting Inhaled Bronchodilators : A Cohort Study Using the UK THIN Primary Care Database.**

[Jara M](#), [Lanes SF](#), [Wentworth C](#), [May C](#), [Kesten S](#).

Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, Connecticut, USA.

BACKGROUND: Use of a long-acting inhaled bronchodilator, either an anticholinergic or a beta-adrenergic receptor agonist (beta-agonist), is recommended for maintenance treatment of chronic obstructive pulmonary disease (COPD). In COPD, the organ system most frequently requiring medical care, other than the respiratory system, is the cardiac system. OBJECTIVES: To compare the risk of total mortality and certain respiratory and cardiac adverse events among users of the two types of recommended long-acting bronchodilators, we conducted a cohort study. Specifically, the study compared the safety of the only approved long-acting anticholinergic, tiotropium bromide, with the single-ingredient long-acting beta-agonists (LABAs) salmeterol or formoterol in a broad population of users. METHODS: We used automated general practitioner data from the UK THIN (The Health Information Network) database as the data source for this study. We used Cox proportional hazards models to compute hazard ratio (HR) estimates and 95% CI controlling for propensity scores comprising various baseline demographic variables, medical therapies and illnesses. RESULTS: The 1061 tiotropium users and 1801 LABA users were similar with regard to risk of total mortality (HR 0.93; 95% CI 0.59, 1.44) and most cardiac events, including angina (HR 0.77; 95% CI 0.37, 1.59), atrial fibrillation or flutter (HR 0.60; 95% CI 0.25, 1.42), myocardial infarction (HR 1.29; 95% CI 0.45, 3.66) and tachycardia (HR 0.66; 95% CI 0.29, 1.51). Though imprecise, there was evidence of a decreased risk of heart failure (HR 0.65; 95% CI 0.37, 1.12) in tiotropium users. As regards respiratory endpoints, the risk of COPD exacerbation (HR 1.15; 95% CI 0.79, 1.67) and pneumonia (HR 1.11; 95% CI 0.38, 3.26) were similar among users of each type of drug, although there was a decreased risk of asthma exacerbation (HR 0.41; 95% CI 0.26, 0.64) in tiotropium users compared with LABA users. CONCLUSIONS: Users of tiotropium and single-ingredient LABA had similar risk of total mortality and cardiovascular endpoints. The decreased risk of asthma exacerbations with tiotropium may be due to residual confounding by indication. Confidence limits for most events include reduced risks for

tiotropium and also small increases in risk. Nevertheless, the point estimates suggest that tiotropium was associated with a lower risk of each cardiac event except myocardial infarction. However, the small number of cases means that further studies are needed to confirm these results.

PMID: 18035867 [PubMed - in process]

---

□ 24: [Drug Saf.](#) 2007;30(12):1161-9.

[Related Articles](#), [Links](#)

### **Analysis of Severe Hepatic Events Associated with Nevirapine-Containing Regimens : CD4+ T-Cell Count and Gender in Hepatitis C Seropositive and Seronegative Patients.**

[Torti C](#), [Costarelli S](#), [De Silvestri A](#), [Quiros-Roldan E](#), [Lapadula G](#), [Cognigni G](#), [Paraninfo G](#), [Castelnuovo F](#), [Puoti M](#), [Carosi G](#); for the BHCC (Brescia HIV Clinical Cohort) Study Group.

School of Medicine, Institute for Infectious and Tropical Diseases, University of Brescia, Brescia, Italy.

**BACKGROUND:** Nevirapine-containing regimens have been associated with a risk of significant elevations of liver transaminase levels. Higher risk in antiretroviral-naïve populations has been related to gender and CD4+ T-cell count (women with CD4+ T-cell counts of  $\geq 250/\text{mm}^3$  or men with CD4+ T-cell counts of  $\geq 400/\text{mm}^3$ , i.e. group at risk). However, recent studies do not confirm this association in HIV populations comprising patients who are antiretroviral-experienced. Moreover, the predictive value of gender and CD4+ T-cell count on the risk of raised transaminase levels has been poorly investigated in populations of patients co-infected with hepatitis C virus (HCV). **METHODS:** Analysis of HIV-positive patients receiving nevirapine-containing regimens for the first time was conducted. Grade  $\geq$ III hepatotoxicity (i.e.  $\geq 5$  x upper limit of normal in alanine aminotransferase or aspartate aminotransferase levels) was the primary endpoint. Univariate and multivariable Cox proportional hazard regression models were separately conducted among HCV-antibody (Ab)-positive and HCV-Ab-negative patients. **RESULTS:** Amongst 905 patients, 49% were HCV-Ab-positive and 79% were antiretroviral-experienced. Grade  $\geq$ III liver transaminase elevations developed in 7.1% of patients, accounting for an incidence of 2.47 (95% CI 1.97, 3.09) per 100 patient-years of follow-up. HCV-Ab reactivity was associated with a 3-fold increase in risk of developing relevant liver transaminase elevations (95% CI 1.75, 5.3;  $p < 0.001$ ), whereas gender and CD4+ T-cell count did not impact significantly. When analysis was performed in HCV-Ab-negative patients, the outcome was independently correlated with the group at risk (hazard ratio [HR] 3.66; 95% CI 1.20, 11.14;  $p = 0.022$ ). By contrast, in HCV-Ab-positive patients, the group at risk was not significantly associated with the outcome. **CONCLUSIONS:** Most of the excess rates of relevant raised transaminase levels in patients prescribed nevirapine-containing regimens could be attributed to HCV co-infection. Gender and CD4+ T-cell count appeared to have a statistically significant impact on the risk of relevant transaminase level elevations in HCV-negative, but not in HCV-positive patients, probably due to a diluting effect of HCV. Incidence of hepatic events after nevirapine-containing regimens did not appear to be a major concern in our cohort of patients who were mainly antiretroviral-experienced and negative for HCV-Ab. Preferably, nevirapine should be avoided in HCV co-infected patients and in males with CD4+ T-cell counts of  $\geq 400/\text{mm}^3$  or females with CD4+ T-cell counts of  $\geq 250/\text{mm}^3$ .

PMID: 18035868 [PubMed - in process]

---

□ 25: [Drug Saf.](#) 2007;30(12):1171-3.

[Related Articles](#), [Links](#)

### **Age- and gender-specific incidence of hospitalisation for digoxin intoxication.**

[Schmiedl S](#), [Szymanski J](#), [Rottenkolber M](#), [Hasford J](#), [Thürmann PA](#).

Philipp Klee-Institute of Clinical Pharmacology, University Witten/Herdecke, Witten, Germany  
HELIOS Klinikum Wuppertal, Wuppertal, Germany.

- 26: [Drug Saf.](#) 2007;30(12):1173-4.

[Related Articles](#), [Links](#)

### The authors' reply.

[Aarnoudse AL](#), [Dieleman JP](#), [Stricker BH](#).

Department of Epidemiology & Biostatistics, Erasmus Medical Center, Rotterdam, The Netherlands  
Inspectorate of Health Care, The Hague, The Netherlands.

PMID: 18035870 [PubMed - in process]

---

- 27: [Breast.](#) 2007 Nov 21 [Epub ahead of print]

[Related Articles](#), [Links](#)

### Role of gemcitabine in metastatic breast cancer patients: A short review.

[Silvestris N](#), [Cinieri S](#), [La Torre I](#), [Pezzella G](#), [Numico G](#), [Orlando L](#), [Lorusso V](#).

Operative Unit of Medical Oncology, Moscati General Hospital, Via per Martina Franca, 74100 Taranto, Italy.

Many active cytotoxic drugs, given according to a number of different regimens are approved for the treatment of metastatic breast cancer patients. However, these therapies have not changed the outcome of patients affected by this malignancy. As a consequence, the balance between chemotherapy-induced side effects and relief of cancer-related symptoms must be carefully considered in this setting.

Gemcitabine is an antimetabolite that is incorporated as a triphosphate into DNA. As a single agent, it yields responses rates ranging from 14% to 37% in chemotherapy-naïve patients and from 12% to 30% in patients previously treated with anthracyclines and/or taxanes. In combination with paclitaxel, it produces a significantly higher response rate (41.4% vs. 26.2%), longer time to progression (6.1 vs. 4 months) and significantly higher overall survival (18.6 vs. 15.8 months) than paclitaxel alone. In addition, a phase III study revealed that gemcitabine plus docetaxel is as effective as capecitabine plus docetaxel, but causes significantly less non-haematologic toxicity. Lastly, in another phase III trial, progression free survival was significantly longer with the combination of gemcitabine plus vinorelbine than with vinorelbine alone (6 vs. 4 months), but without a significant difference in overall survival; the incidence of haematologic toxicity was higher in the group treated with combined therapy. Novel gemcitabine combinations are being investigated in phase II studies.

PMID: 18037292 [PubMed - as supplied by publisher]

---

- 28: [Vaccine.](#) 2007 Nov 8 [Epub ahead of print]

[Related Articles](#), [Links](#)



**"All that palsies is not Bell's "-The need to define Bell's palsy as an adverse event following immunization.**

[Rath B](#), [Linder T](#), [Cornblath D](#), [Hudson M](#), [Fernandopulle R](#), [Hartmann K](#), [Heininger U](#), [Izurieta H](#), [Killion L](#), [Kokotis P](#), [Oleske J](#), [Vajdy M](#), [Wong V](#); [The Brighton Collaboration Bell's Palsy Working Group](#).

University Children's Hospital Basel, Basel, Switzerland.

Bell's palsy has been reported as an adverse event following immunization (AEFI). Review of the

published literature reveals that several characteristics have been used to describe Bell's palsy, which differ significantly from author to author. Evidently, the definition of "Bell's palsy" remains controversial, and consensus between different medical subspecialties is urgently needed. The Brighton Collaboration has formed an international working group with representatives of neurology, otorhinolaryngology, pediatrics, electrophysiology, pharmacology, pharmaceutical and biotech industry as well as regulatory agencies to create a case definition of Bell's palsy as an AEFI.

PMID: 18037542 [PubMed - as supplied by publisher]

---

- 29: [Neurology](#). 2007 Nov 27;69(22):E27-9.

[Related Articles](#), [Links](#)



**Seizure medications and their side effects.**

[Karceski SC](#).

PMID: 18040007 [PubMed - in process]

---

- 30: [Pharmacoepidemiol Drug Saf](#). 2007 Nov 27;16(12):1313-1314 [Epub ahead of print]

[Related Articles](#), [Links](#)



**Studies of diabetes, thiazolidinediones, and coronary heart disease.**

[Walker AM](#), [McAfee AT](#), [Koro C](#).

i3 Drug Safety, Waltham, MA, USA.

PMID: 18041104 [PubMed - as supplied by publisher]

---

- 31: [Pharmacoepidemiol Drug Saf](#). 2007 Nov 27;16(12):1273-1274 [Epub ahead of print]

[Related Articles](#), [Links](#)



**Is there a connection between methylphenidate and cancer in youth?**

[Zito JM](#), [Safer DJ](#).

University of Maryland, Pharmaceutical Health, Professor of Pharmacy and Psychiatry, Services Research, 220 Arch St., Baltimore, Maryland, USA.

PMID: 18041105 [PubMed - as supplied by publisher]

---

- 32: [Pharmacoepidemiol Drug Saf](#). 2007 Nov 27;16(12):1268-1272 [Epub ahead of print]

[Related Articles](#), [Links](#)



**Methylphenidate use in children and risk of cancer at 18 sites: results of surveillance analyses.**

[Oestreicher N](#), [Friedman GD](#), [Jiang SF](#), [Chan J](#), [Quesenberry C Jr](#), [Habel LA](#).

Division of Research, Kaiser Permanente Medical Care Program, Oakland, CA, USA.

PURPOSE: A recent report linked methylphenidate (MPH) use in children to cytologic abnormalities in

plasma lymphocytes, a possible cancer biomarker. The purpose of this study was to investigate the association of MPH use and childhood cancer risk. METHODS: Using automated pharmacy databases and the SEER-affiliated cancer registry of the Kaiser Permanente Medical Care Program (KPMCP), we compared cancer rates at 18 sites among 35 400 MPH users who received it before age 20 to rates among KPMCP membership (age, sex, and calendar year standardized). Medical records of MPH exposed cancer cases were reviewed to identify the presence of established risk factors. RESULTS: There were 23 cancers among MPH users, versus 20.4 expected (standardized morbidity ratio, SMR = 1.13, 95% confidence interval (0.72, 1.70)). Given the small number of cancers, site-specific SMR estimates were imprecise. Only one SMR was statistically significant at the  $p < 0.05$  level, which given the number of comparisons is consistent with the absence of a true association at any site. MPH use was associated with increased risk of lymphocytic leukemia (SMR = 2.64 (1.14, 5.20)), based on eight observed cases). The medical records of these exposed cases did not reveal any lymphocytic leukemia risk factors (prior cancer, radiotherapy or chemotherapy, or Down syndrome). CONCLUSIONS: Our results are consistent with no moderate or strong association between MPH use and cancer risk in children, although our ability to examine dose and duration of use or risk at specific sites was limited by small numbers. Further study of MPH use and lymphocytic leukemia risk is needed to determine whether our results are due to chance alone. Copyright (c) 2007 John Wiley & Sons, Ltd.

PMID: 18041106 [PubMed - as supplied by publisher]

---

□ 33: [Pharmacoepidemiol Drug Saf.](#) 2007 Nov 27;16(12):1314-1316 [Epub ahead of print]

[Related Articles](#), [Links](#)



### **A comparison of pioglitazone and rosiglitazone for hospitalization for acute myocardial infarction in type 2 diabetes.**

[Gerrits CM](#), [Bhattacharya M](#), [Manthena S](#), [Baran R](#), [Perez A](#), [Kupfer S](#).

Takeda Global Research & Development, Inc., Deerfield, IL.

PMID: 18041107 [PubMed - as supplied by publisher]

---

□ 34: [Pharmacoepidemiol Drug Saf.](#) 2007 Nov 28 [Epub ahead of print]

[Related Articles](#), [Links](#)



### **Lung cancer and regular use of aspirin and nonaspirin nonsteroidal anti-inflammatory drugs.**

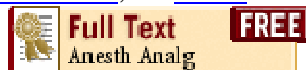
[Kelly JP](#), [Coogan P](#), [Strom BL](#), [Rosenberg L](#).

Slone Epidemiology Center of Boston University, Boston, MA, USA.

PURPOSE: Lung cancer is the leading cause of cancer death in the US. There is evidence of a reduced risk of some cancer sites associated with use of aspirin (ASA) and nonaspirin nonsteroidal anti-inflammatory drugs (NANSAIDs). Our objective was to examine the association of regular use of ASA and NANSAIDs with lung cancer. METHODS: A hospital-based case-control study of 1884 incident cases of lung cancer and 6251 controls with noncancer diagnoses. Use of ASA and NANSAIDs was considered 'regular' if it occurred on  $\geq 4$  days/week and lasted for  $\geq 3$  months. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals. RESULTS: The OR for regular use of ASA was 1.1 (0.9-1.4), and the corresponding estimate for regular NANSAID use was 1.0 (0.7-1.3). There was no evidence of decreased risk within strata of age, sex, years of education, or interview year. Examining the association within strata of duration of use, recency of use, cigarette smoking status, pack-years of cigarette smoking, or histologic type of cancer produced no ORs significantly different from 1.0. CONCLUSIONS: The hypothesis that regular use of ASA or NANSAIDs reduces the risk of lung cancer is not supported by the present data. Copyright (c) 2007 John Wiley & Sons, Ltd.

- 35: [Anesth Analg](#). 2007 Dec;105(6):1693-700, table of contents.

[Related Articles](#), [Links](#)



**The 8-item Short-Form Health Survey and the physical comfort composite score of the quality of recovery 40-item scale provide the most responsive assessments of pain, physical function, and mental function during the first 4 days after ambulatory knee surgery with regional anesthesia.**

[Bost JE](#), [Williams BA](#), [Bottegal MT](#), [Dang Q](#), [Rubio DM](#).

Center for Research on Health Care, and Department of Anesthesiology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213, USA. bostje@upmc.edu

**BACKGROUND:** We evaluated the validity and responsiveness of three instruments: the numeric rating scale (NRS) pain score, the 8-item Short-Form Health Survey (SF-8), and the 40-item Quality of Recovery from Anesthesia (QoR) Survey in 154 outpatients undergoing anterior cruciate ligament reconstruction (ACLR). The objective was to provide a robust psychometric basis for outcome survey selection for surgical outpatients undergoing regional anesthesia without general anesthesia.

**METHODS:** Patients undergoing ACLR with a standardized spinal anesthesia plan were randomized to receive a perineural catheter with either placebo injection-infusion, or injection-infusion with levobupivacaine. Patients completed the NRS, SF-8, and QoR instruments for four postoperative days to evaluate pain, physical function, and mental function. **RESULTS:** Regarding pain, neither the NRS nor the QoR offered advantages over the SF-8. Regarding physical function, the QoR physical independence composite offered no advantage over the SF-8 physical component summary. The QoR physical comfort composite assessed short-term changes in treatment-related side effects, and thus provided information not covered by the SF-8. Regarding mental function, the SF-8 mental component summary and QoR emotional state composite showed little change over the four days, although the latter measure showed higher responsiveness to change. **CONCLUSIONS:** For ACLR outpatients receiving regional anesthesia, the SF-8 is sufficient to assess postoperative pain and physical function. Adding the QoR physical comfort composite will help assess short-term side effects.

Publication Types:

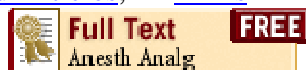
- [Research Support, N.I.H., Extramural](#)
- [Research Support, Non-U.S. Gov't](#)

PMID: 18042869 [PubMed - in process]

---

- 36: [Anesth Analg](#). 2007 Dec;105(6):1793-804, table of contents.

[Related Articles](#), [Links](#)



**Cardiovascular thromboembolic adverse effects associated with cyclooxygenase-2 selective inhibitors and nonselective antiinflammatory drugs.**

[Joshi GP](#), [Gertler R](#), [Fricker R](#).

Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, Texas 75390-9068, USA. girish.joshi@utsouthwestern.edu

**BACKGROUND:** Concerns of increased cardiovascular (CV) thromboembolic adverse effects from nonsteroidal antiinflammatory drugs (NSAIDs, both nonselective [NS]-NSAIDs and cyclooxygenase

[COX]-2 selective inhibitors) have prevented their use despite numerous benefits. **METHODS:** In this descriptive review, we critically examine the randomized, active- and placebo-controlled studies, observational trials, and meta-analyses evaluating the CV adverse effects associated with long-term and short-term use of COX-2 selective inhibitors and NS-NSAIDs. The potential mechanisms for these CV effects are also presented. **RESULTS:** Although the studies evaluating the CV risks have limitations, there appears to be an increased CV risk with both COX-2 selective inhibitors and NS-NSAIDs, particularly in high-risk patients. Therefore, the United States Food and Drug Administration has given a similar "boxed" warning highlighting the potential for increased risk of CV events associated with their use. Nevertheless, there are differences in the CV risks between COX-2 selective inhibitors (e.g., higher CV risk with rofecoxib than celecoxib) as well as differences in the CV risks between individual NS-NSAIDs (e.g., higher CV risks with diclofenac than naproxen). **CONCLUSIONS:** Until long-term, prospective, randomized, adequately powered, clinical studies in relevant patient populations have been completed, the CV risks associated with the use of NSAIDs, especially in high-risk patients, will likely continue to be controversial. Nevertheless, the benefits of their short-term (e.g., perioperative) use in patients without CV risks probably outweigh their potential CV adverse effects. Finally, careful risk/benefit assessment should be undertaken and both COX-2 selective inhibitors and NS-NSAIDs should be used with caution in patients with CV risk factors.

PMID: 18042885 [PubMed - in process]

---

□ 37: [Ther Drug Monit.](#) 2007 Dec;29(6):687-710.

[Related Articles](#), [Links](#)



### **Clinically Important Drug Interactions Potentially Involving Mechanism-based Inhibition of Cytochrome P450 3A4 and the Role of Therapeutic Drug Monitoring.**

[Zhou SF](#), [Xue CC](#), [Yu XQ](#), [Li C](#), [Wang G](#).

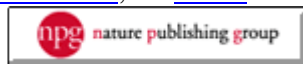
From the \*Division of Chinese Medicine, School of Health Sciences, WHO Collaborating Center for Traditional Medicine, RMIT University, Victoria, Australia; †Department of Nephrology, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; and ‡Key Lab of Drug Metabolism and Pharmacokinetics, China Pharmaceutical University, Nanjing, China.

Cytochrome P450 (CYP) 3A4 is the most abundant enzyme of CYPs in the liver and gut that metabolizes approximately 50% currently available drugs. A number of important drugs have been identified as substrates, inducers, and/or inhibitors of CYP3A4. The substrates of CYP3A4 considerably overlap with those of P-glycoprotein. Both CYP3A4 and P-glycoprotein are subject to inhibition and induction by a number of factors. Mechanism-based inhibition of CYP3A4 is characterized by NADPH-, time-, and concentration-dependent enzyme inactivation occurring when some xenobiotics or drugs are converted by CYPs to reactive metabolites. Such an inhibition of CYP3A4 is caused by chemical modification of the heme, the protein, or both as a result of covalent binding of modified heme to the protein. To date, the identified clinically important mechanism-based CYP3A4 inhibitors mainly include macrolide antibiotics (eg, clarithromycin and erythromycin), anti-HIV agents (eg, ritonavir and delavirdine), antidepressants (eg, fluoxetine and fluvoxamine), calcium channel blockers (eg, verapamil and diltiazem), steroids and their modulators (eg, gestodene and mifepristone), and several herbal and dietary components. The inactivation of CYP3A4 by drugs often causes unfavorable and long-lasting drug-drug interactions and probably fatal toxicity, depending on many factors associated with the enzyme, drugs, and the patients. Clinicians are encouraged to have a sound knowledge of drug-induced, mechanism-based CYP3A4 inhibition; take proper cautions, and perform close monitoring for possible drug interactions when using drugs that are mechanism-based CYP3A4 inhibitors. To minimize drug-drug interactions involving mechanism-based CYP3A4 inhibition, it is necessary to choose safe drug combination regimens, adjust drug dosages appropriately, and conduct therapeutic drug monitoring for drugs with narrow therapeutic indices.

PMID: 18043468 [PubMed - as supplied by publisher]

---

□ 38: [Clin Pharmacol Ther.](#) 2007 Nov 28 [Epub ahead of print]



## Post-marketing Strategies for Medicines.

[Breckenridge A.](#)

1Medicines and Healthcare Products Regulatory Agency Market Towers, London, UK.

PMID: 18043682 [PubMed - as supplied by publisher]

---

- 39: [N Engl J Med](#). 2007 Nov 29;357(22):2217-9.



## Bolstering the FDA's drug-safety authority.

[Schultz WB.](#)

Zuckerman Spaeder LLP, Washington, DC, USA.

PMID: 18046024 [PubMed - in process]

---

- 40: [N Engl J Med](#). 2007 Nov 29;357(22):2219-21.



## In defense of pharmacoepidemiology--embracing the yin and yang of drug research.

[Avorn J.](#)

Harvard Medical School and Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, USA.

PMID: 18046025 [PubMed - in process]

---

- 41: [Arch Phys Med Rehabil](#). 2007 Dec;88(12):1547-60.

## Comparison of the effectiveness of amitriptyline and gabapentin on chronic neuropathic pain in persons with spinal cord injury.

[Rintala DH](#), [Holmes SA](#), [Courtaide D](#), [Fliess RN](#), [Tastard LV](#), [Loubser PG](#).

Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX 77030, USA.  
drintala@bcm.tmc.edu

**OBJECTIVE:** To test the hypotheses that both amitriptyline and gabapentin are more effective in relieving neuropathic pain than an active placebo, diphenhydramine. **DESIGN:** Randomized, controlled, double blind, triple crossover 8-week trial. **SETTING:** Veterans Affairs medical center. **PARTICIPANTS:** Community dwelling adults with spinal cord injury (N=38) were recruited by telephone, letters, and flyers. **INTERVENTION:** Eight-week trial each of amitriptyline, gabapentin, and diphenhydramine. **MAIN OUTCOME MEASURES:** Pain intensity measured with a 10-cm visual analog scale (VAS) and an 11-point (0-10) numeric rating scale (NRS) and depressive symptomatology measured with the Center for Epidemiologic Studies Depression Scale-Short Form (CESD-SF). **RESULTS:** Baseline VAS scores for participants with low (< 10) CESD-SF scores was 4.61 and for those with high scores (> or = 10) it was 7.41. At week 8, in participants with high baseline CESD-SF

scores, amitriptyline (mean, 4.21) was more effective than diphenhydramine (mean, 6.67; P=.035), and there was a nonsignificant trend suggesting that amitriptyline may be more effective than gabapentin (mean, 6.68; P=.061). Gabapentin was no more effective than diphenhydramine (P=.97). There was no significant difference among the medications for those with lower CESD-SF scores. Results could not be attributed to dropout rates, order or dose of medications, amount of medication taken for breakthrough pain, or side effects. CONCLUSIONS: Amitriptyline is more efficacious in relieving neuropathic pain than diphenhydramine at or below the level of spinal cord injury in people who have considerable depressive symptomatology.

Publication Types:

- [Research Support, U.S. Gov't, Non-P.H.S.](#)

PMID: 18047869 [PubMed - in process]

---

42: [Arch Phys Med Rehabil](#). 2007 Dec;88(12):1601-5.

[Related Articles](#)

### **Clinical analysis of risk factors for falls in home-living stroke patients using functional evaluation tools.**

[Wada N](#), [Sohmiya M](#), [Shimizu T](#), [Okamoto K](#), [Shirakura K](#).

Division of Rehabilitation Medicine, Gunma University Hospital, Gunma, Japan. [nwada@med.gunma-u.ac.jp](mailto:nwada@med.gunma-u.ac.jp)

OBJECTIVES: To identify risk factors associated with falls in home-living stroke patients and to predict falls using patient information and functional evaluation tools. DESIGN: Cohort study. SETTING: Community. PARTICIPANTS: We recruited 101 home-living stroke patients who had hemiparesis and could walk independently with or without supporting devices. Disease duration ranged from 1 to 22 years (mean, 6.1 y). INTERVENTIONS: Not applicable. MAIN OUTCOME MEASURES: The score of each item of the Stroke Impairment Assessment Set (SIAS), and the FIM instrument, sex, age, duration of disease, stroke type, affected side of the body, frequency of rehabilitation, use of sedatives, and Mini-Mental State Examination score were evaluated and the occurrence of falls was observed prospectively for 12 months. RESULTS: Forty-five (44.6%) participants fell, 20 of whom fell repeatedly. A logistic model for predicting falls was refined until it included 4 predictors: memory score on the FIM, range of motion of the lower extremities on the SIAS, duration of disease, and affected side. The predictive value of the logistic model was 86.7%. CONCLUSIONS: Evaluation tools were useful for predicting falls and devising preventive strategies in the high-risk group of home-living stroke patients.

PMID: 18047874 [PubMed - in process]

---

43: [J Clin Pharmacol](#). 2007 Dec;47(12):1532-9.

[Related Articles](#)

### **Effect of high-dose metronidazole on pharmacokinetics of oral budesonide and vice versa: a double drug interaction study.**

[Dilger K](#), [Fux R](#), [Röck D](#), [Mörrike K](#), [Gleiter CH](#).

Department of Clinical Pharmacology, Institute of Pharmacology and Toxicology, University Hospital Tübingen, Otfried-Müller-Str. 45, D-72076 Tübingen, Germany; e-mail: [christoph.gleiter@med.uni-tuebingen.de](mailto:christoph.gleiter@med.uni-tuebingen.de).

Recent case reports suggest that addition of high-dose metronidazole might be associated with elevated

plasma concentrations of substrates of cytochrome P450 (CYP) 3A. Because patients with fistulizing Crohn's disease benefit by using high doses of metronidazole for prolonged periods, this study's primary aim was to evaluate the effect of high-dose metronidazole on the pharmacokinetics of oral budesonide, a sensitive substrate of CYP3A commonly prescribed in acute inflammatory bowel disease. Twelve healthy adults received 1.5 g metronidazole per day over 1 week. The CYP3A-dependent metabolic profile of an oral dose of budesonide (3 mg) and that of endogenous cortisol were compared intraindividually before and after administration of metronidazole. There was neither a significant effect of high-dose metronidazole on the area under the plasma concentration-time curve (AUC) of budesonide (90% confidence interval, 79%-115%) nor on the AUC ratios of 6beta-hydroxybudesonide/budesonide and 16alpha-hydroxyprednisolone/budesonide. In parallel, metronidazole did not significantly alter formation of 6beta-hydroxycortisol. Vice versa, budesonide did not affect the AUC of metronidazole (90% confidence interval, 91%-100%). The authors conclude that in contrast to concomitant intake of other imidazoles such as ketoconazole, concomitant intake of metronidazole may not lead to serious safety concerns due to elevated systemic concentrations of the glucocorticoid budesonide.

PMID: 18048573 [PubMed - in process]

---

□ **44:** [Pharmacoepidemiol Drug Saf.](#) 2007 Nov 30 [Epub ahead of print]  
[Related Articles](#)

### **Potentially inappropriate prescribing to hospitalised patients.**

[Radošević N](#), [Gantumur M](#), [Vlahović-Palčevski V](#).

Department of Pharmacology, University of Rijeka Medical School, Rijeka, Croatia.

**PURPOSE:** The objective of this study was to evaluate the prevalence of potential drug-drug interactions (DDIs) in hospitalised patients in correlation with patient's age and number of drugs prescribed and to determine the prevalence of inappropriate drugs prescribed to elderly patients. **METHODS:** Drugs prescribed during 1 day to all hospitalised patients at seven wards of Department of Medicine in University Hospital Rijeka were recorded by reviewing patient medical charts. Potential DDIs were evaluated using a list of potentially harmful drug combinations compiled from the literature. Beers criteria were used to identify potentially inappropriate medications in patients aged 65 years or older. **RESULTS:** The study included 225 patients that received a total of 1301 drugs. Twenty-two percent of the patients receiving drug therapy were prescribed drug combinations that are potentially harmful. The most common potentially harmful drug combination was an ACE inhibitor with a potassium supplement (33.9% of all combinations). In the multivariate analysis, age and number of drugs are significantly associated with potential DDIs ( $r = 0.8629$ ). One quarter of elderly patients received a drug potentially inappropriate considering their age. The most commonly prescribed potentially inappropriate drug was amiodarone, followed by diazepam. **CONCLUSION:** Polypharmacy and older age have been proven to be important risk factors for potential drug interactions. We identified a high rate of prescribing potentially inappropriate medications among elders. Results of this study indicate that particular caution should be given when prescribing drugs to patients already receiving drugs and to elderly patients, considering the risk of drug-related problems. Copyright (c) 2007 John Wiley & Sons, Ltd.

PMID: 18050360 [PubMed - as supplied by publisher]