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### FDA Reviews Bisphosphonate Safety

By John J. Cush, MD and Kathryn Dao, MD

On September 9, 2011 the FDA convened a joint session of the Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committees to examine the safety of bisphosphonates. These advisory committees examined overall bisphosphonate safety, the risk of atypical femoral fractures and osteonecrosis of the jaw, esophageal cancer risk and whether a “drug holiday” may lessen any of these risks.

There are currently four approved drugs in this class – Actonel (risedronate), Reclast (zoledronic acid), Boniva (ibandronate) and Fosamax (alendronate), with the latter also available in generic forms. While all warn of osteonecrosis of the jaw, atypical femoral fractures, esophagitis and esophageal ulcers, none carries any warning about an esophageal cancer risk. The manufacturers of these agents presented the benefits of bisphosphonate therapy and were uniformly opposed to label changes on issues where evidence is lacking.

Bisphosphonates have been available since 1995, and today they are widely-prescribed medications; about seven people out of every 100 in the U.S. received a prescription for a bisphosphonate with nearly \$8 billion in sales in 2008.

The following issues were discussed after review of published and manufacturer data:

1. The long-term safety of bisphosphonate therapy for the treatment and prevention of osteoporosis has not been established. In 2011 the FDA required labeling changes to reflect that the optimal duration of use hasn’t been determined and that the need for continued bisphosphonate therapy should be re-evaluated periodically.
2. The risk of osteonecrosis of the jaw (ONJ) has been incorporated in product labeling since 2005, however there is no clear evidence of clear risk. Kaiser Permanente conducted the “Predicting Risk of Osteonecrosis with Bisphosphonate Exposure” ([PROBE](#)) study and found nine cases of stage 1

or 2 ONJ among 8,572 treated patients. Notably, 7 of these 9 patients had taken the drugs for more than 4 years. Such findings suggest that longer use of oral bisphosphonates may be an important risk factor for ONJ.

3. Since 2010, an increasing number of atypical femur fractures have been associated with bisphosphonate use. An American Society for Bone and Mineral Research task force has concluded that the risk is small, but real. During this advisory meeting the FDA identified 126 Medwatch reports of atypical subtrochanteric fractures that may be bisphosphonate-related, but didn’t have enough data to draw any firm conclusions. FDA review of epidemiological data found atypical fractures appear to have a strong association with bisphosphonates, but there is no agreement on the extent to which cumulative use of bisphosphonates increases the risk of atypical fractures.
4. Whether long-term use of bisphosphonates (>3 yrs) warrants a “drug holiday” to help prevent fractures in patients was discussed. FDA reviewers analyzed pooled data on patients taking three different types of bisphosphonates and determined that patients who took a bisphosphonate for three to five years and then stopped had the same fracture incidence as those who continued taking the drug, leading them to conclude there may be no benefit in continuing therapy beyond five years. A small study of 32 patient taking a bisphosphonate for seven years before being switched to a placebo or back on the bisphosphonate for five years, and then were switched back to open-label bisphosphonate. The data from this small pilot study appear to support a “drug holiday” for “some period of time.” “In light of the potential risks that may be associated with long-term use of bisphosphonates for the treatment and/or prevention of osteoporosis, the sum of available long-term efficacy data appears to suggest that bisphosphonate therapy could be safely discontinued for some period of time,” the reviewers concluded.

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### Risk of Legionella and Listeria: Boxed Warning Update for TNF inhibitors

The FDA announced on September 7, 2011 that all TNF alpha inhibitors (TNFi) will have updated boxed warnings citing risk for serious and sometimes fatal infections from *Legionella* and *Listeria*. This builds upon the 2008 expanded warnings for fungal infections, including histoplasmosis, blastomycosis and coccidioidomycosis. A recent FDA review of bacterial infections in patients treated with TNF (from 1999-2010) identified 80 cases of *Legionella* pneumonia associated with TNFi; 14 patients died. Median age of patients was 56 years (range 25-85 years). The most frequent indication for use of TNFi in these patients was RA (65%), duration of use 10.4 months (range < 1-73 months). Many were on methotrexate, corticosteroids, or both. Legionnaires’ disease is a systemic infectious disease primarily involving the lungs, but may have extrapulmonary manifestations (e.g., FUO, serositis, endocarditis, myocarditis, pyelonephritis, abscesses).

In the same FDA Medwatch search, 26 cases of *Listeria* were found; including cases of meningitis, bacteremia, endophthalmitis, and sepsis. There were seven deaths found in both phase 2 and 3 clinical trials and postmarketing studies. Additional nonfatal cases of *Listeria* have occurred in clinical trials, the agency warned.

Reports of *Listeria* outbreaks in the US have recently appeared. *MMWR* (September 30, 2011/60;1-2) states there has been at least 21 deaths and 109 infections which have been linked to cantaloupes from Jensen Farms in Colorado. In addition, California-based *True Leaf Farms* has announced a recall of chopped romaine lettuce that also may be contaminated with *Listeria* bacteria. It is typically a food-borne organism that can be isolated from soil, water, and decaying vegetation. Other recent large outbreaks involved frankfurters and Mexican cheese. Common features of *Listeria* in the elderly and immunocompromised include septicemia and meningitis, but may also present as milder flu-like illness or febrile gastroenteritis. Patients older than 65 years are at increased risk for infection, the FDA warned.

Clinicians should monitor patients taking TNF-alpha inhibitors for signs and symptoms of serious infection and should report any adverse events associated with the medication to the [MedWatch Safety Database](#).  

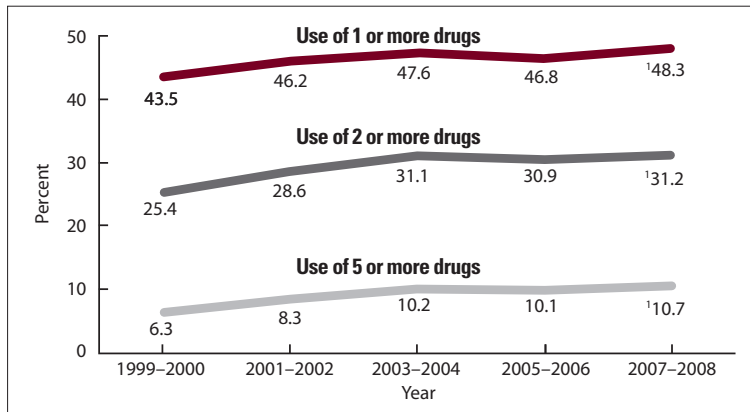
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5. No consensus was achieved regarding the risk of esophageal cancer associated with long-term bisphosphonate use. Two studies from the General Practice Research Database (one a retrospective cohort design (Cardwell et al. JAMA 2010;304:657-63 PMID: 20699457), and the other a nested case-control design (Green et al. BMJ 2010 Sept) arrived at different conclusions. Similarly the reviewers had opposing views as to whether this risk should be communicated to practitioners by adding an esophageal cancer risk to bisphosphonate labeling.

The panel voted 17-6 in favor of making changes to the current label, but failed to find consensus on what those conclusions should be. Overall, most felt that bisphosphonate efficacy may wane with time (e.g., four – five years) and that rare adverse events (i.e., ONJ or atypical femoral fractures) may also be related to the duration of therapy. Clearly more research is needed to better define these risks and measures needed to minimize them. **DSQ**

## Fast Facts

**Figure 1. Trends in the percentage of persons using prescription drugs: United States, 1999-2008**



<sup>1</sup>Significant linear trend from 1999-2000 through 2007-2008.

NOTE: Age adjusted by direct method to the year 2000 projected U.S. population.

SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey.

<b>2.3 Billion</b>	Number of drugs ordered
<b>13,000</b>	Number of prescription drugs on the market
<b>200+</b>	Number of drug labeling changes made in 2011 thus far
<b>74%</b>	Percent of physician visits involving drug therapy
<b>48%</b>	Percent of persons using at least one prescription drug in the past month

Sources: [www.cdc.gov/nchs/fastats/drugs.htm](http://www.cdc.gov/nchs/fastats/drugs.htm)

[www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm238512.htm](http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm238512.htm) (Accessed Sept 2011)

### Most frequently prescribed therapeutic classes:

Analgesics  
Antihyperlipidemics  
Antidepressants

Source: <http://www.cdc.gov/nchs/fastats/drugs.htm>

**DSQ**

## In the News

**NSAIDs May Increase Risk for Atrial Fibrillation (Afib).** In a recently published study, NSAIDs were found to increase the risk for Afib/flutter. The case-control study reviewed inpatient and outpatient diagnoses of Afib/flutter from Northern Denmark (population 1.7 million). The incidence rate ratio (IRR) for Afib/flutter was 1.33 (95%CI 1.26-1.41) for nonselective NSAIDs and 1.50 (95%CI 1.42-1.59) for COX2 inhibitors. After adjusting for age, sex and other risk factors for Afib/flutter, the IRR was 1.17 (95%CI 1.10-1.24) for nonselective NSAIDs and 1.27 (95% CI 1.20-1.34) for COX2 inhibitors. Compared to non-users, the association with Afib/flutter was strongest for new users with a 40-70% increase in relative risk. The editorial accompanying the study pointed out that potential confounders were missing from the study such as obesity, which is an established risk factor for Afib and often associated with OA, one of the most common indications for NSAID use. (BMJ 2011; 343:d3450. PMID:21727167) **Editor's note:** NSAIDs have been associated with various renal and cardiovascular adverse effects by inhibiting COX derived prostaglandins, thereby expanding plasma volume, and increasing peripheral resistance. These physiologic changes may themselves likely increase the risk of atrial fibrillation or flutter. Of note, a case-control study of patients in the United Kingdom published in 2010 cited similar results in patients who develop Afib while on NSAIDs (IRR 1.44, 95%CI 1.08-1.91), long term users having the largest risk. (Arch Intern Med. 2010;170(16):1450-1455 PMID:20837831)

**NSAIDs Increase Risk for Spontaneous Abortions Early in Pregnancy.** A recent case-control study published in the Canadian Medical Association Journal reported that NSAID use is linked to a greater than 2 fold increase in miscarriage. The study reported 4705 case patients who had spontaneous abortions since 1997; 352 (7.5%) who had prescription NSAID exposure compared to 1213 (2.6%) of 47,050 control subjects. After adjusting for potential confounders, odds ratio [OR] for spontaneous abortion were 2.43 with any NSAID (95% CI 2.12-2.79), 3.09 with diclofenac (95% CI 1.96-4.87), 2.64 with naproxen (95% CI 2.12-3.28), 2.21 with celecoxib (95% CI 1.42-3.45), 1.83 for rofecoxib (95%CI 1.24-2.7), 2.19 with ibuprofen (95%CI 1.61-2.96), 2.64 for combination NSAIDs (95% CI 1.59-4.39). There was no apparent dose-response effect. Study limitations include lack of data on OTC formulation of NSAIDs during pregnancy and lack of information for why NSAIDs were used and on covariables as smoking and BMI. The authors also noted that the study only covered 36% of pregnant women in Quebec, suggesting a sampling bias. CMAJ, Epub Sept 2011 PMID:21896698

**Recommended Maximum Tylenol Daily Dose Drops to 3000 mg.** McNeil Consumer Healthcare, a Johnson & Johnson company announced on July 28, 2011 that Tylenol (acetaminophen) will have a lower recommended daily dose to reduce the risk of accidental overdose. The labeling will reflect that the recommended daily maximum for Extra Strength Tylenol 500 mg tablets is 6 per day (down from 8 per day). The company informed the FDA that new labeling changes will take effect in the last quarter of this year. Lower daily maximum recommendations for other Tylenol products will be included in the packaging next year. (<http://www.tylenol.com/page2.jhtml?id=tylenol/news/newdosing.inc>)

**Increase in Hip fracture after Cessation of Hormone Replacement Therapy (HRT).** After the publication of the Women's Health Initiative Trial on HRT in 2002, millions of women abruptly stopped HRT. A longitudinal cohort study was published recently by Southern California Kaiser Permanente to examine the impact of this decision on hip fractures. 80,955 women were followed from July 2002 to Dec 2008. After adjusting for age, race and bisphosphonate use; the study found that women who stopped HRT were at 55% greater increase for hip fracture and lower BMD (as early as two years) compared to women who continued on HRT. These findings are comparable to the Million Women Study which demonstrated fracture risk increased three years after HT discontinuation (JAMA 2004). Menopause. 2011 Jul 19. PMID:21775911

**Breastfeeding reduces hip fracture risk postmenopause.** A September 2011 report from *Journal of Bone and Mineral Research* suggests breastfeeding may reduce the risk of hip fracture in postmenopausal women. Bjørnerem and colleagues surveyed 4681 women (50 - 94 years of age) between 1994 - 2010 to study the effect of parity

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and breastfeeding on fracture risk. In addition, 3748 women provided information on the duration of their breastfeeding for analysis. With over 14.5 years of follow-up, fractures of the hip, wrist or proximal humerus occurred at a rate of 7.8, 11.4 and 21.3 fractures per 1000 person-years, respectively. Women who breastfed were 50% less likely to suffer a hip fracture and were 27% less likely to sustain a fragility fracture than women who did not breast feed, though they were at a similar risk of wrist fracture. *J Bone Miner Res.* Epub Aug 2011 [PMID:21898594](#)

**Supreme Court Ruling on Generic Drug Safety.** In June 2011, the U.S. Supreme Court issued a decision (5 to 4 opinion -- *Pliva v. Mensing*) that found generic drug makers are immune from civil claims alleging "failure to warn" about potential drug risks as generic drugs are required by federal law to use the same warnings as their brand name counterparts. Bob Billings, head of the generic industry trade group, stated, "As the Supreme Court recognized in this decision, assessing liability based on label content that is beyond the control of the generic manufacturer places the generic manufacturer in the impossible position of defending the content of a label that they are required by law to use but prevented by law from changing." Concerns have been voiced that in instances where brand name products are no longer marketed, it is unclear who will be responsible for postmarketing safety surveillance and revisions to product labels should new safety signals surface. According to a publication by the Texas Medical Liability Trust, *The Reporter* (2011, vol 4), the balance between cost and safety is becoming more challenging for physicians and this ruling "bodes poorly for both patients and physicians." If a patient is injured due to inadequate generic drug labeling, they will no longer be able to pursue civil claims against the drug makers; their only options are to accept their loss or file a claim against the prescribing doctor. DⓄQ

**Websites for Drug Safety**

<b>DrugCite.com</b> <a href="http://www.drugcite.com/">www.drugcite.com/</a>	Drug safety news and user-friendly searchable dataset derived from the FDA Adverse Event Reporting System (AERS). This website allows users to search the kind and frequency of adverse events reported for a brand name drug.
<b>AdverseEvents.com</b> <a href="http://adverseevents.com/index.php">http://adverseevents.com/index.php</a>	A drug safety site devoted to both patients and healthcare professionals. You do not have to register to use this searchable database with over 4,000 approved medications and over 500,000 annual medication adverse events.
<b>Drug Information Service (University of Utah)</b> <a href="http://healthcare.utah.edu/pharmacy/alerts/">http://healthcare.utah.edu/pharmacy/alerts/</a>	The latest drug alerts and warnings.
<b>Medicines and Healthcare Products Regulatory Agency</b> <a href="http://www.mhra.gov.uk/Safetyinformation/index.htm">www.mhra.gov.uk/Safetyinformation/index.htm</a>	UK regulatory agency responsible for medication and device safety. This site has safety warnings, alerts and recalls, and a drug safety update.
<b>Drug Safety Communications from the FDA</b> <a href="http://www.fda.gov/Drugs/DrugSafety/ucm199082.htm">www.fda.gov/Drugs/DrugSafety/ucm199082.htm</a>	Recent communications and alerts on drug safety. Also medication guides, drug shortages, recalls, postmarketing safety information for patients and providers.
<b>Information on drug shortages</b>	<a href="http://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm">www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm</a> <a href="http://www.ashp.org/shortages">www.ashp.org/shortages</a> <span style="float: right;">DⓄQ</span>

**FDA MedWatch**

**Benzocaine gels/liquids and methemoglobinemia.** Fatal cases of methemoglobinemia have been associated with OTC benzocaine gels and liquids applied to the gums/mouth. These sprays are marketed under brand names as Hurricaine, Cetacaine, Exactacain and Topex. Methemoglobinemia is not related to the amount of product applied and in many cases, after a single administration of benzocaine spray. Currently, labels are not required to carry this warning. (April 2011)

**Tylenol Extra Strength Caplets recalled due to odor.** McNeil Consumer Healthcare is recalling Tylenol Extra Strength Caplets, 225 count bottles, lot ABA619 due to a small number of musty, moldy odor reports. The odor has been linked to the presence of trace amounts of a chemical known as 2,4,6-tribromoanisole (TBA). While not considered to be toxic, TBA can generate an offensive odor and has been associated with temporary and non-serious gastrointestinal symptoms. (June 2011)

**Hydrochlorothiazide (HCTZ) associated with acute angle closure glaucoma.** HCTZ, a sulfonamide derivative drug, may cause an acute transient myopia and acute angle closure glaucoma. Typical clinical presentation includes bilateral involvement with blurring of vision over minutes to hours, nausea or vomiting, red eye, and headache. The risk is increased in patients with history of sulfonamide or penicillin allergy. *Editor's note: Other sulfonamides which have been linked to glaucoma include topiramate (Topamax), celecoxib (Celebrex), and furosemide (Lasix).* (June 2011)

**Avoid Mobic (meloxicam) suspension and Kayexalate coadministration.** Cases of intestinal necrosis (possibly fatal) have been described in patients who received concomitant sorbitol and Kayexalate (sodium polystyrene sulfonate). Due

to the presence of sorbitol in MOBIC Oral Suspension, use with Kayexalate is not recommended. *Editor's note: Consuming large amounts of medicines containing sorbitol may induce a hyperosmolar diarrhea. Other commonly used liquid medications that may contain large amounts of sorbitol include: acetaminophen, amantadine, cimetidine, dexamethasone, furosemide, lithium, metoclopramide, propranolol, and theophylline.* (July 2011)

**False positive drug test for amphetamines associated with bupropion medications.** Patients taking Wellbutrin XL (bupropion hydrochloride) Extended-Release Tablets or Aplenzin (bupropion hydrobromide) may develop a false positive urine drug screen for amphetamines. Patients should be alerted to this fact. (July 2011)

**Fluconazole and congenital malformations.** New warnings were issued by the FDA regarding use of fluconazole in pregnant women based on case reports describing a rare pattern of distinct congenital anomalies (brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs, long bones, arthrogryposis, and congenital heart disease) in infants exposed in-utero to chronic, high dose maternal fluconazole (400-800 mg/day) during the first trimester. These anomalies were similar to those seen in animal studies. Currently, there are no adequate studies of fluconazole in pregnant women; available human data do not suggest an increased risk of congenital anomalies following a single maternal dose of 150 mg for vaginal candidiasis. Based on this information, the pregnancy category for fluconazole indications (other than vaginal candidiasis) has been changed from category C to category D. The pregnancy category for a single, low dose of fluconazole has not changed and remains category C. (August 2011)

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**High Dose Celexa Can Induce Arrhythmias.** The FDA warns that citalopram (Celexa) should not be used at doses greater than 40 mg/day due to risk for arrhythmias. The drug at higher doses may prolong the QT interval leading to fatal arrhythmias, including torsade de pointes. Risk is further augmented by low potassium and magnesium levels. Studies did not show benefits in doses greater than 40 mg/day, although the drug label previously stated that certain patients may require doses of 60 mg/day. (August 2011)

**Reclast Contraindicated in Severe Renal Impairment.** The drug's new labeling update warns of risk for kidney failure. Cases of acute renal failure requiring dialysis or having fatal outcomes after Reclast infusions have been reported to the FDA. The revised label cited that Reclast is contraindicated in patients whose creatinine clearance is < 35 cc/min or who have evidence of acute renal impairment. The label also recommends screening patients prior to infusions in order to identify at-risk individuals. (Sept 2011) **DSQ**

**Common Drugs: MSK Drug Interactions**

According to WebMD (4/21/11), \$57 billion is spent annually on care of musculoskeletal (MSK) related disorders. MSK disorders rank fifth behind cardiovascular disease (\$95.6 B), trauma (\$74.3B), cancer (\$72.2B) and mental disorders (\$72.1B) in expenditures. In 2010 there were four billion prescriptions written in the USA, 78% of these were for generic drugs. Table 1 is a list of the most often prescribed drugs in 2010 (as reported by the IMS Institute for Healthcare Informatics) and drug interactions of greatest interest to the rheumatologist.

**Table 1. Most Prescribed Drugs of 2010**

Drug	Prescriptions (millions)	MSK Interactions or Adverse Events (AE) of Interest
<b>Hydrocodone</b>	131.2	Leading cause of prescription drug deaths (actually more common than traffic accident deaths)
<b>Simvastatin</b>	94.1	High dose simvastatin (80 mg/day) has been associated with myopathy and rhabdomyolysis
<b>Lisinopril</b>	87.4	ACE inhibitors and NSAIDs may cause renal impairment, renal failure or blunting of the antihypertensive effect
<b>Synthroid</b>	70.5	High dose of levothyroxine may be associated with hip fracture risk
<b>Amlodipine</b>	57.2	ACE inhibitors and NSAIDs may cause renal impairment, renal failure or blunting of the antihypertensive effect
<b>Omeprazole</b>	53.4	PPI may lower Mg++ levels; may increased risk of hip, wrist, or spine fractures (risk is greatest in those > 50yrs or with PPI use > 1 year)
<b>Azithromycin</b>	52.6	Is safer than clarithromycin in patients taking colchicine. May be used in combination to treat disseminated <i>Mycobacterium avium</i> complex (MAC) disease or alone as prophylaxis/prevention of MAC in at risk persons (HIV, patients on TNF inhibitors)
<b>Amoxicillin</b>	52.3	Rarely interacts to reduce renal clearance of MTX. Mostly a problem with much higher, antineoplastic doses and not a problem with low dose weekly MTX (unless there is renal insufficiency)
<b>HCTZ</b>	47.8	Rare reports of myalgias and chills. Skin reactions include erythema annular centrifugum, acute eczematous dermatitis, and morbilliform and leukocytoclastic vasculitis

DSQ

**Safety Signals: References & Reviews**

Compiled by Kathryn H. Dao and John J. Cush from the Baylor Research Institute, Dallas TX

1. Incidence of Tuberculosis Among Korean Patients with Ankylosing Spondylitis Who Are Taking Tumor Necrosis Factor Blockers. Kim EM, et al; J Rheumatol. 2011;38:2218-23. [PMID: 21844149](#)  
 → 919 TNF-naïve AS patients and 354 TNF inhibitors (TNFi) treated patients were compared to the general population (a mean TB incidence rate of 69.8/100,000 person-years). No cases of TB occurred in the etanercept-treated AS cohort and all cases occurred in those treated with monoclonal antibodies. In this endemic area, inflammatory disease and TNFi imparted a 4.4 and 8 fold increased risk of TB, respectively.
2. Effect of Pregnancy on Ankylosing Spondylitis: A Case-Control Study; Lui NL, et al; Journal of Rheumatology (Aug 2011). [PMID: 21844140](#)  
 → 19 patients with AS (35 pregnancies) were compared with 33 controls (77 pregnancies) for pain and outcomes. Pain improved in 51% of AS patients, predominantly in the first trimester. Overall, pregnancy did not aggravate disease activity or severity in AS.
3. Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials. Ryan C, et al. =JAMA. 2011;306:864-71. [PMID:21862748](#)  
 → This meta-analysis analyzed 22 clinical trials (10183 patients) of anti-IL-12/23 and anti-TNF drugs in patients with psoriasis and failed to show a statistically significant increase in CV events with biologics. However, the study may have been underpowered to detect these rare events.
4. Lower gastrointestinal perforation in rheumatoid arthritis patients treated with conventional DMARDs or tocilizumab: a systematic literature review. Gout T, et al. Clin Rheumatol. Aug 2011. [PMID:21833686](#)

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- In the tocilizumab clinical trials, the lower GI perforation rate was 1.9 per 1,000 PY. This compares with that seen in steroids and anti-TNF agents, with rates of 3.9 per 1,000 PY (95% CI 3.1-4.8) and 1.3 per 1,000 PY (95% CI 0.8-1.9), respectively. The risk of diverticular perforation may be slightly higher with tocilizumab compared with conventional DMARDs or anti-TNF agents, but lower than that for steroids. PMID:21833686
- The DRESS syndrome: a literature review. Cacoub P, et al. Am J Med. 2011;124:588-97. PMID: 21592453  
→ Drug Reaction with Eosinophilia and Systemic Symptom (DRESS) is a severe adverse drug-induced reaction. A total of 44 drugs were associated. Carbamazepine was the most frequently reported. Other common causes included allopurinol, sulfasalazine and dapsone. Hypereosinophilia, liver involvement, fever, skin rash and lymphadenopathy are the hallmark features.
  - Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: a nationwide cohort study. Schjerning Olsen AM, et al. Circulation. 2011; 123:2226-35. PMID:21555710  
→ NSAID treatment duration and risk of cardiovascular (CV) disease in patients with history of prior MI. 83,677 patients were studied. NSAID treatment was significantly associated with an increased risk of death/recurrent MI (HR, 1.45; 95% confidence interval, 1.29 to 1.62).
  - Infections in patients treated with tumor necrosis factor antagonists: incidence, etiology and mortality in the BIOBADASER registry. Pérez-Sola MJ, et al. Med Clin (Barc). 2011 Apr 21. PMID: 21514606  
→ Most frequent infections were skin infection (12.18 cases/1,000 PY), pneumonia (5.97 cases/1,000 PY), cystitis (3.92 cases/1,000 PY), tuberculosis (3.51 cases/1,000PY) and arthritis (3.76 cases/1,000 PY). Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Pseudomonas aeruginosa and Salmonella spp. emerged as important pathogens. Pneumonia, sepsis, tuberculosis, abdominal infection and endocarditis were associated with an increased mortality.
  - Opioid dose and drug-related mortality in patients with nonmalignant pain. Gomes T, et al. Arch Intern Med. 2011;171:686-91. PMID: 21482846  
→ 607,156 people on opioids included 498 eligible patients whose deaths were related to opioids. A daily dose of 200 mg or more of morphine (or equivalent) was associated with a nearly 3-fold increase in the risk of opioid-related mortality
  - Prospective Evaluation of Analgesic Use and Risk of Renal Cell Cancer (RCC). Eunyoung Cho, et al. Arch Intern Med. 2011;171:1487-1493. PMID: 21911634  
→ The association between analgesic use and RCC was studied in the Nurses' Health Study and the Health Professionals Follow-up Study. After 16 - 20 years of follow-up with >127,000 subjects, they documented 333 RCC cases. Whereas aspirin and acetaminophen not associated with a RCC risk, regular use of nonaspirin NSAIDs was associated with an increased RCC risk (RR 1.51 (95% CI, 1.12-2.04) that increased further with longer duration NSAID therapy.
  - Anabolic agents and bone quality. Sibai T, et al. Clin Orthop Relat Res. 2011;469:2215-24. PMID: 21132409  
→ Review of the safety and effects of anabolic agents (including PTH, strontium, prostaglandin agonists, sclerostin, etc.) on bone quality and osteoporosis. DSQ

## EULAR 2011 Safety Update

**Azathioprine & lupus pregnancy.** Saavedra et al (OP0172) performed a 180 patient retrospective observational analysis of lupus patients who were or were not exposed to azathioprine (AZA). Patients who received AZA were more likely to be younger, in their 1<sup>st</sup> pregnancy, have renal disease and preeclampsia and fewer full term deliveries. The authors surmised that lupus patients can safely receive AZA during pregnancy without a significant increase in stillbirths, miscarriages, preterm deliveries or fetal malformations.

**Etanercept and RA mortality.** Emery, et al. (#LB0007) examined RA patients from the British Biologics Registry (BSRBR) who were followed for >5 yrs and had a DAS28 >4.2 at entry. When ETN patients (n=3740) were compared to those on DMARDs alone (1365), a higher mortality rate was not observed with ETN. ETN patients had more severe disease and less comorbidity, but overall trended towards a lower mortality rate (Hazard Ratio ~0.6-0.8) after several models of multivariate analysis.

**Mortality and TNF inhibitors.** 6322 RA patients receiving first time anti-TNF agents (adalimumab, etanercept, or infliximab) between 2003-2008 were studied for all-cause mortality by Simard et al (OP0158). Although there were 211 deaths (3.3%), no difference in the mortality rates were seen when comparing outcomes of patients treated with adalimumab, etanercept, or infliximab.

**Cancer risk with DMARDs.** The British biologics registry (BSRBR) studied 3727 RA DMARD-treated, biologic-naïve patients (FRI0338). A 50% increased cancer

rate was seen (SIR = 1.48, 95% CI 1.25-1.73) compared to the general population). Lymphoma, melanoma and lung cancer were increased in RA patients receiving DMARDs only.

**Cancer risk with TNF inhibitors.** The Danish DANBIO registry (FRI0203) studied 13,699 RA and psoriatic arthritis patients and compared those treated with TNF inhibitors (n=5,598) to those where TNFi naïve. No increased risk of cancer was observed for those receiving TNFi (RR = 1.03 (95% confidence interval 0.82-1.30) versus anti-TNF naïve patients. No increase risk of nonmelanomatous skin cancer and lymphoma was observed. (*Editors' note: it's important to note the comparator group is RA patients not receiving TNFi; the citation above demonstrates that RA patients have an increase risk of certain malignancies. This study suggests that the use of TNFi does not further augment the cancer risk due to RA alone.*)

**GI Perforations in RA.** Curtis et al (OP0159) retrospectively queried a claims database for hospitalizations due to GI perforations among 143,433 RA patients between 2001-09. GI perforation occurred in 0.5% of patients, with 6.6% of these patients dying during admission. Risk factors associated with GI perforations included a prior history of diverticulitis, corticosteroid use, age >65 yrs, with higher Charlson Comorbidity scores and non-methotrexate DMARD use. Whereas a history of diverticulosis did not increase risk, diverticulitis did increase risk.

To review these and other abstracts from the London 2011 EULAR meeting go to [www.abstracts2view.com/eular/](http://www.abstracts2view.com/eular/). DSQ

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*This issue has been reviewed by members of the ACR Drug Safety Committee and Communications and Marketing Committee.*

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