

Welcome, New House Staff

On behalf of the Department of Pharmacy Services at the University of Washington Medical Center, Harborview Medical Center, Seattle Cancer Care Alliance, and UW Medicine Neighborhood Clinics, I would like to welcome you. We look forward to working with you during your residency.

You will be receiving copies of the *Drug Therapy Topics* newsletter on a monthly basis. This newsletter is a source of current pharmacotherapy-related information as well as a major communication between the Department of Pharmacy Services, the Pharmacy and Therapeutics Committee, and the medical staff. It is intended, in part, to keep you updated on additions and deletions to the medical centers' formulary, along with changes in policies and procedures as approved by the Pharmacy and Therapeutics Committee. Your input into its content is welcome.

The medical centers' *Drug Formulary* provides key information regarding drug availability, along with procedures pertaining to medication use. You will be provided with a personal copy of the formulary. For expanded and updated clinical details on all drugs and for "alerts" regarding formulary drugs, you may also access the formulary and the UW Drug Information Center website electronically at <http://uw.pnrx.org>.

If you have any questions regarding pharmacy services, please ask the clinical pharmacist on the unit or in the clinic (see other side of this insert for a directory) or call one of the following pharmacy phone numbers. Again, a sincere welcome from all of us.



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Drugs That Induce Heart Failure: An Overview (Part 2 of 2)

Part 1 of “Drugs That Induce Heart Failure: An Overview” by Dr. Rudy, D.V.M., R.Ph. was published in the July 2007 issue of *Drug Therapy Topics* (Vol. 36 No. 7). An electronic copy is available at <http://uw.pnrx.org>.

Editor’s Note: Adverse drug reactions experienced by HMC, SCCA, or UWMC patients and reported via Patient Safety Net (PSN) are reviewed quarterly by the UW Pharmacy and Therapeutics Committee. Following the Committee’s review, a literature-based companion article regarding some aspect of adverse drug reactions is published in this newsletter. It is hoped that these articles will be useful tools to remind prescribers of the fundamental principle of pharmacology that states, “No drug has only one action.” By reminding prescribers to be alert to the appearance of undesired and unintended actions of drugs, therapeutic outcomes may be improved and adverse events minimized. If you have a patient you believe is experiencing an Adverse Drug Reaction, please report it via Patient Safety Net.

Controversy exists as to whether tricyclic antidepressant (TCA) drugs cause heart failure. The effects of TCAs on heart rate, blood pressure, and cardiac rhythm are well known. Experimental animal studies indicate a direct effect on cardiac contractility.²⁵ Older studies indicate that cardiac function might be impaired with TCA use, but more recent studies fail to demonstrate such an association.² Slørdahl, et al. state that evidence to date indicating that TCAs may cause heart failure is unconvincing.² However, it is recommended that patients with existing heart failure be monitored closely if treatment with a TCA is started.²

The atypical antipsychotic drug clozapine has been associated with potentially fatal myocarditis and cardiomyopathy. To date, approximately 41 cases have been reported in the literature.^{26,27} Based upon data from clozapine sales, the risk of myocarditis caused by clozapine is estimated to be approximately 1 per 2,000 to 1 per 500 treated patients.^{26,27}

It has been postulated that glucocorticoids may precipitate or worsen heart failure via stimulation of mineralocorticoid receptors.² Mineralocorticoid receptor activation might exacerbate heart failure by increasing sodium and fluid retention and by promoting fibrotic remodeling in the heart.² Two recent epidemiological studies looked at the risk of heart failure in association with glucocorticoid therapy.^{28,29} Souverein, et al. found that current glucocorticoid use was associated with an increased risk of heart failure.²⁹ Wei, et al. found that exposure to glucocorticoids was associated with a dose-dependent increased risk of heart failure.²⁸ Slørdahl, et al. points out that although the above two studies were observational in nature and that confounding cannot be ruled out, they both indicate an increased risk of heart failure during glucocorticoid therapy.² He also states that clinical studies are needed to address this important issue.

Data from the FDA Adverse Event Reporting System database describes potential cases of heart failure associated with the use of the antifungal drug itraconazole.³⁰ Because most of the patients had pre-existing cardiovascular disease or were taking other drugs concurrently, it is not possible to establish a causal relationship between use of the drug and heart failure. However, early clinical studies and animal data suggest that itraconazole may have negative inotropic effects.² Therefore, patients on itraconazole therapy should be carefully monitored for signs of heart failure.³⁰ Additionally, the treatment of onychomycosis in patients with ventricular dysfunction is contraindicated. Four cases of cardiomyopathy associated with the use of the antifungal drug amphotericin B have been reported in the literature.³¹⁻³³ In all four cases, heart failure symptoms resolved after discontinuation of the drug.

The appetite suppressants fenfluramine (withdrawn from the market) and dexfenfluramine (withdrawn from the market) alone, or in combination with phentermine, have been shown to induce pulmonary hypertension and/or heart valve disease that may result in heart failure. In a European case control study, data from 95 cases of pulmonary hypertension and 355 controls were analyzed.³⁴ The risk of pulmonary hypertension when an appetite suppressant such as fenfluramine or dexfenfluramine was taken was found to be increased 6.3-fold. If the exposure to the drug was for >3 months, the risk was increased 23-fold.

These drugs may produce cardiac valve disease in a frequency range of 0.1-38%.² The reasons for this wide incidence variation include use of different drug combinations, drug dose and treatment duration differences, and sensitivity differences in the testing methodologies used to detect the adverse effects.² In a study of 1,835 patients treated with fenfluramine plus phentermine, Jollis, et al. showed that the prevalence of aortic regurgitation in treated patients was significantly different from the prevalence in the

**Summary of
Drugs Associated
with Cardiotoxicity**
(adapted from reference #2)

Cardiomyopathy

- **Amphotericin B***
- Anthracyclines
- Capecitabine
- **Clozapine***
- Cyclophosphamide
- Doxorubicin
- Epirubicin
- Etanercept
- Fluorouracil
- Infliximab
- Interferon alpha-2
- Interleukin-2
- **Itraconazole***
- Mitoxantrone
- Trastuzumab

Fluid overload

- COX-2 inhibitors
- **Glucocorticoids***
- NSAIDs
- Pioglitazone
- Rosiglitazone
- Troglitazone
(withdrawn from market)

Pulmonary hypertension

- **Dexfenfluramine***
(withdrawn from market)
- **Ergotamine***
- **Fenfluramine***
(withdrawn from market)
- **Methylsergide***
- **Phentermine***

Heart-valve abnormalities

- **Cabergoline***
- **Dexfenfluramine***
(withdrawn from market)
- **Ergotamine***
- **Fenfluramine***
(withdrawn from market)
- **Methylsergide***
- **Pergolide***
(withdrawn from market)
- **Phentermine***

* See text for discussion

control group of patients *only* after treatment for >6 months.³⁵ For patients treated for 90-180 days with the drugs, the prevalence was 4.5% and for the control group the prevalence was 3.6%. With treatment for >720 days, the prevalence of aortic regurgitation in the treated group of patients increased to 17.4%.

The cardiac valve function changes seen are generally considered to be irreversible, but usually do not progress after the drug has been discontinued.² Gardin, et al. did clinical and echocardiographic follow-up on 711 patients who had taken dexfenfluramine or fenfluramine/phentermine for 1-2 years.³⁶ In more than 90% of the patients, the heart lesions did not change, 5-6% improved, and less than 4% continued to deteriorate.

Fenfluramine and dexfenfluramine act via stimulation of brain serotonergic pathways. Interestingly, the changes in heart valve anatomy seen with exposure to these appetite suppressants are similar in appearance to those observed in patients with serotonin-producing carcinoid tumors.² Slørdahl, et al. postulates that the common pathogenic factor leading to the similar changes observed in both conditions could be an increase in serotonin production in the systemic circulation.² To date, sibutramine, a new appetite suppressant that acts via norepinephrine/serotonin reuptake inhibition, has not been linked to changes in cardiac valve structure or the development of pulmonary hypertension.^{2,37}

The ergotamine derivative anti-migraine drugs methysergide and ergotamine have been linked to aortic, mitral, and tricuspid heart-valve lesions. Reactions to methysergide were first described more than 30 years ago.² More recently, a few reports involving ergotamine exposure have appeared in the literature.^{38,39} The fact that both drugs are partial serotonin agonists may explain why the valvular effects observed resemble those seen in patients who took dexfenfluramine/fenfluramine or who have serotonin-producing carcinoid tumors.²

The dopamine receptor agonists pergolide and cabergoline, used to treat Parkinson's disease, have both been associated with heart-valve lesions and heart failure. Because these drugs are both ergot derivatives, it is plausible that the heart-valve lesions seen on histological exam after exposure to these drugs resemble those observed in patients with carcinoid tumors.² Slørdahl, et al. report a total of eight cases of heart failure associated with pergolide exposure and one case associated with cabergoline therapy.² Two recently published studies describe the association between these dopamine agonists and valvular heart disease.^{40,41} Zanettini, et al. performed an echocardiographic prevalence study in 155 patients taking dopamine agonists.⁴¹ Sixty-four patients took pergolide, 49 patients took cabergoline, 42 took non-ergot-derived dopamine agonists, and 90 were control subjects. Clinically important valve regurgitation (defined as moderate to severe, grade 3 to 4) in any valve was identified with significantly greater frequency in patients taking cabergoline (28.6%) or pergolide (23.4%) but not in patients taking non-ergot-derived dopamine agonists (0%) or control subjects (5.6%) Patients treated with cabergoline or pergolide who had grade 3 to 4 regurgitation of any valve were shown to have received a higher mean cumulative dose of the drugs than patients with lower regurgitation grades. In March 2007, pergolide was withdrawn from the market due to its association with these serious adverse cardiac effects.

Although heart failure is primarily caused by cardiovascular disease, a large number of medications from a diverse range of drug classes have the potential to cause or worsen pre-existing heart failure. Because of the widespread use of some of these medications, it is important for healthcare providers to be aware of these issues when prescribing for patients, particularly those with pre-existing cardiovascular disease or other confounding factors that could make them more susceptible to development of adverse cardiac effects after the initiation of drug therapy.

References available upon request.

Pharmacy & Therapeutics Committee Actions

Formulary Additions	Dosage Form(s), Strength(s), & Cost [†]	Therapeutic Classification	Use	Usual Adult Starting Dose*
Bosentan (Tracleer[®])	Tablet: 62.5mg, 125mg	Endothelin receptor antagonist	Pulmonary arterial hypertension	62.5mg po twice daily
	Added to formulary with use restricted to hospitalized patients receiving the drug prior to admission. The manufacturer restricts ambulatory dispensing to the Tracleer Access Program.			
Doxylamine (generic)	Tablet: 25mg	Antihistamine	Nausea/vomiting in pregnancy	25mg po 3 or 4 times daily
Progesterone (Endometrin[®])	Suppository, vaginal: 100mg	Hormone	Embryo/fetal support	100mg vaginally 2 or 3 times daily
Other Actions				
Radiology Guidelines Revised	Revisions to the UWMC Radiology guidelines for the administration of contrast agents based on calculated creatine clearance were approved.			
Guidelines for Darbepoetin	Revisions to the UW Medicine guidelines for administering erythropoietin agents were approved.			

* Refer to product labeling for full prescribing information. † Contact pharmacy for information on drug costs.

Get Your Copy of the 2007/2008 UW Medicine Drug Formulary

The 2007/2008 *UW Medicine Drug Formulary* is available in both an electronic and a hard copy pocket-sized book. The *Formulary* lists the drug products available for prescribing to UW patients. The *e-Formulary* is updated during the third week of every month following UW Medicine Pharmacy and Therapeutics Committee meetings. The Formulary can be accessed electronically from HealthLinks by entering the word “formulary” in the search box. To download the drug list, choose the “UW Medicine Drug Formulary for Palm” or “UW Medicine Drug Formulary for PocketPC” hyperlink. Downloading is simple. If assistance is needed or if a printed copy of the Drug Formulary is desired, contact druginfo@u.washington.edu or call 598-6612.

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drug therapy topics