



World of Drug Information

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CURRENT CLINICAL ISSUES

ACPE Continuing Education Now Available

The *World of Drug Information* will now offer American Council on Pharmaceutical Education (ACPE) approved pharmacy continuing education credit. For some time now each issue of the *World of Drug Information* has contained a lead article on a clinical therapeutics issue. The clinical therapeutic article will now carry ACPE-approved pharmacy continuing education credit. We anticipate that most articles will provide one hour (0.1 CEU) of credit. Directions for obtaining continuing education credit for this issue's article, "Beta-blockers in chronic heart failure," appear on page 6. Participants need only fill out and return the answer sheet with a nominal fee of U.S. \$5.00 to cover the cost of processing and mailing. We are delighted to increase the value of the *World of Drug Information* to our readers. Please let me know if you have any comments about this new program.

Hazel H. Seaba, Director, <hazel-seaba@uiowa.edu>

Beta-Blockers in Chronic Heart Failure

Goal: To increase awareness of the evidence for benefits from use of beta-blockers in patients with chronic heart failure.

Objectives:

- Describe traditional treatment options for chronic heart failure.
- Contrast the pharmacological mechanism of action of the four main classes of drug therapies for chronic heart failure.
- Describe the results of the CIBIS II and MERIT-HF trials.
- List the characteristics of heart failure patients that would be favorable to benefit from the use of beta-blockers.
- List characteristics that may be considered a contraindication to beta-blocker use.

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In the United States, 4.8 million people are afflicted with heart failure, and approximately 400,000 to 700,000 new cases are reported each year. Approximately 1.5% to 2.0% of the population has heart failure, and the prevalence increases to 6% to 10% in patients more than 65 years of age. Heart failure is the only major cardiovascular disorder that is currently increasing in prevalence. In part the increased prevalence is due to improved survival after acute myocardial infarction and the general aging of the U.S. population; however, there is clearly a need to focus on effective prevention and treatment of this serious condition. Approximately 250,000 patients die as a result of heart failure each year, and the number of deaths has increased sixfold in the past

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40 years. The risk of death is 5% to 10% annually in patients with mild symptoms and as high as 40% in patients with advanced disease. Patients with heart failure are frequently hospitalized, and in patients 65 years of age and older, heart failure is the leading cause of hospitalization (Packer, 1999).

Twenty years ago diuretics and digitalis were the primary therapeutic options for treatment of chronic heart failure (CHF). These treatments offered little or no expectation of stopping the downhill course of the disease. These drugs were successful in promoting better pump function and improvement in clinical symptoms; yet they seemed to have adverse long-term effects on the heart with no decrease in mortality. Within the past decade the spectrum of treatment options broadened to include two other drug classes: angiotensin converting enzyme (ACE) inhibitors and more recently, beta-blockers.

Recent advances in our understanding of the pathophysiology of heart failure and new developments in the therapy of this disorder have greatly expanded the information base on which to make decisions.

Traditional CHF Practice Guidelines

By definition, heart failure involves dysfunction in the heart's pumping action. As heart failure progresses, it tends to become increasingly more difficult to manage. The competition between the heart and the kidneys to compensate for the loss of cardiac output, compounded by the release of vasoconstrictive stress hormones such as norepinephrine, complicates the treatment strategy of chronic heart failure.

Digitalis

Digoxin, the oldest treatment in alleviating the symptoms of heart failure and increasing exercise tolerance, remains a commonly prescribed first-line treatment. Digoxin's mechanism of action is a positive inotropic action and suppression of increased neurohormonal activity. The results of a large, long-term study indicate that adding digoxin to other drugs decreases the rate of

hospitalization, but has neither beneficial nor adverse effects on survival (Garg, 1997).

Diuretics

Diuretics play an important role in heart failure treatment. Heart failure patients are fluid-retentive and require diuretics to alleviate the volume overload that can lead to backup congestion and peripheral edema. The mechanism of action of this class of drugs is to increase renal excretion of water and sodium and relieve symptoms of heart failure, but diuretics do not stop the progression of the underlying disease. Diuretics most often used clinically are those that act on the loop of Henle, such as furosemide. The most common adverse effect of this treatment is potassium depletion. This side effect can be corrected through potassium supplements, concurrent use of ACE inhibitors or potassium-sparing diuretics (amiloride, triamterene and spironolactone). A thiazide diuretic can be added if loop diuretics and dietary sodium restriction are not adequate in reducing volume overload (Brater, 1998).

ACE Inhibitors

ACE inhibitors inhibit formation of angiotensin II, a potent vasoconstrictor, enhance the action of kinins and reduce aldosterone secretion. These effects produce a decrease in total peripheral resistance, pulmonary vascular resistance and decrease sodium and water retention. Cardiac index, cardiac output, stroke volume and exercise tolerance are increased in patients with heart failure. In the last 10 years, a number of trials have demonstrated that ACE inhibitors reduce mortality as well as the incidence of morbidity and are considered standard therapy (Weiner, 1997). The hemodynamic or cardioprotective effects alone cannot solely explain the results of ACE therapy. The cardioprotective effect can be recognized based upon ACE inhibitors' ability to alter the course of left ventricular remodeling that occurs in chronic heart failure. Although this process of remodeling is slowed, there is no evidence that ACE inhibitors lead to reversal of the remodeling process. Reverse remodeling occurs only when both angiotensin II and adrenergic activity are blocked (Francis, 1993).

Emerging Treatment Options

Beta-Blockers

Only recently has the addition of beta-blockers to chronic heart failure treatment been viewed as a powerful tool in reducing mortality. In fact, beta-blockers have traditionally been viewed as inappropriate treatment for heart failure, despite some evidence of their benefit from various studies over the past 20 years. The Cardiac Insufficiency Bisoprolol Study (CIBIS), published in 1994, investigated the effect of bisoprolol in heart failure (Lechat, 1994). The CIBIS trial was the first large-scale study of beta-blocker treatment in heart failure that studied mortality as the main endpoint. Patients received both ACE inhibitors and diuretics, and patients already on digoxin remained on that treatment. A total of 641 patients with chronic heart failure of various causes and a

left ventricular ejection fraction of <40% were entered into this placebo-controlled, randomized study. Bisoprolol therapy resulted in a 20% reduction in mortality; however, this did not have statistical significance because the trial was underpowered and many of the patients did not reach a sufficient dose of study drug.

The Metoprolol in Dilated Cardiomyopathy (MDC) trial examined death and the need for a transplant as endpoints. The trial evaluated 383 patients with idiopathic dilated cardiomyopathy randomized to metoprolol or placebo with maximum doses of 150 mg of metoprolol daily. The metoprolol group had 34% fewer endpoints (95% CI -6% to 62%, $p = 0.058$) than the placebo group. Investigators found that metoprolol reduced the need for transplant, indicating that metoprolol prevented the progression of pump failure in the heart (Waagstein, 1993).

Carvedilol, a nonselective beta-blocker with alpha-blocking activity, is currently the only FDA-approved beta-blocker for the treatment of heart failure. In a one-year, double-blind trial involving 366 patients with mild chronic heart failure and reduced left ventricular ejection fraction, the clinical endpoints were death, hospitalization or sustained increases in medications to control the patient's heart failure. This study (Colucci, 1996) utilized carvedilol 6.25 to 25 mg bid with either an ACE inhibitor or digitalis or both. Clinical progression was decreased in those patients taking carvedilol (11%) vs. placebo (21%) with a 48% reduction in disease progression (RR 0.52, 95% CI 0.32–0.85, $p = 0.008$). The rationale behind the use of carvedilol is its multiple pharmacological actions. One of its actions is the blockade of beta-receptors in

The benefits of beta-blockers have been demonstrated as additive to the benefits of ACE inhibitors and diuretics.

cardiac tissue, which protects the heart against overstimulation by noradrenaline. Easing this stimulation or blocking it completely entails significant risk if the workload of the heart is not also decreased simultaneously. The addition of alpha-blocking activity, specific to carvedilol, may consequently decrease some of the adverse effects of beta-blockers due to the balancing vasodilatation caused by the alpha-blocking activity. The resulting decrease in blood pressure allows the heart to pump against less force. Carvedilol has been shown to have additional properties such as antioxidant effects to scavenger free radicals. The role of this mechanism is yet to be determined as an asset in heart failure treatment. Third-generation beta-blockers, such as carvedilol, are not without adverse effects. The common adverse drug reactions are induction of bronchospasm, bradycardia, heart block, diarrhea, nausea, hyperglycemia, fluid retention and symptomatic hypotension within the first few weeks of treatment.

The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) evaluated 2,647 ambulatory patients with clinically stable

New York Heart Association (NYHA) class III or IV heart failure (Dargie, 1999). Patients were randomized to placebo or a 1.25-mg starting dose of bisoprolol that was increased to 10 mg daily (if tolerated) over three months. Over 95% of the patients in this study were also receiving diuretics and an ACE inhibitor. CIBIS II was stopped early after the second interim analysis (mean follow-up 1.3 years) because bisoprolol showed a significant mortality benefit. The estimated annual mortality rate was 8.8% in the bisoprolol group and 13.2% in the placebo group ($p < 0.0001$). The number of patients needed to be treated (NNT) for one year to prevent one death is 23. Patients in the bisoprolol group also had a statistically significant 15% reduction in all-cause hospitalization. Subgroup analysis demonstrated that the treatment benefits were independent of the severity or cause of heart failure. This large, well-designed trial supports the addition of a beta-blocker to standard therapy with a diuretic and an ACE inhibitor in patients with stable moderately severe and severe CHF caused by systolic dysfunction. These results should not be extrapolated to patients with severe NYHA class IV symptoms with recent instability.

The most recently published large trial in this area is the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). This trial (Hjalmarson, 1999) included 3,991 patients with NYHA class II–IV heart failure who were receiving a combination of a diuretic and an ACE inhibitor. Patients were randomized to placebo or metoprolol controlled release 12.5 or 25 mg once daily increased to a target dose of 200 mg once daily over eight weeks if tolerated. This study was also stopped early because the second interim analysis after a mean follow-up of one year demonstrated a significant benefit of treatment. All-cause mortality was 7.2% in the metoprolol group and 11.0% in the placebo group, relative risk 0.66 (95% CI 0.53–0.81, $p = 0.0062$). The number needed to be treated for one year to prevent one death is 27.

Now that beta-blockers are becoming an accepted treatment for chronic heart failure, studies are being done to determine which beta-blockers are most effective in treatment. A prospective, randomized, one-year comparison of metoprolol and carvedilol in CHF was done in a patient population with moderate to severe symptoms already on triple drug therapy (Kukin, 1999). Sixty-seven patients were on constant doses of ACE inhibitors and digoxin for a minimum of six weeks and constant doses of diuretics for a minimum of two weeks. Patients were given a baseline evaluation that included vital signs, exercise tests, a measure of oxidative stress and quality-of-life questionnaires. Patients were randomly assigned to receive metoprolol 6.25 mg daily or carvedilol 3.125 mg bid for one week; then doses were titrated to a target dose of 25 mg bid. At four, six and 12 months at the maintenance dose, all clinical, exercise and quality-of-life measurements were repeated. Both metoprolol and carvedilol were well tolerated, and there were no

significant differences between treatments in any of the measures including oxidative stress. Ejection fraction increased over six months from $18 \pm 6.3\%$ to $23 \pm 8.7\%$ ($p < 0.005$) with metoprolol and from $19 \pm 8.5\%$ to $25 \pm 9.9\%$ ($p < 0.0005$) with carvedilol ($p = \text{NS}$ between groups). All the patients completing the study demonstrated improvement in each clinical and exercise parameter, providing further confirmation that beta-blockers are beneficial in chronic heart failure.

At the present time, two other studies are recruiting patients to further study beta-blockers in the treatment of heart failure. The Carvedilol Prospective Randomized Cumulative Survival trial (COPERNICUS) will enroll 2,000 patients and is investigating whether patients with unstable and more advanced heart failure (NYHA Class III–IV) will have improved survival when on beta-blockers. The Carvedilol or Metoprolol European Trial (COMET), which plans to enroll more than 3,000 patients, will compare metoprolol and carvedilol to determine the survival benefits of these two drugs with different pharmacological effects.

Conclusion

The beta-blockade offered by such medications as bisoprolol, metoprolol and carvedilol has demonstrated mortality and morbidity benefits in patients with chronic heart failure. The benefits of beta-blockers have been demonstrated as additive to the benefits of ACE inhibitors and diuretics. Beta-blocker studies also have shown an increase cardiac output, ejection fraction and exercise capacity. The most effective treatment strategy for this class of CHF medications is start low and go slow. With the immediate pharmacological effect of worsening of symptoms, as well as suppression of left ventricular function, these medications require careful monitoring when initiated, and appropriate adjustments in diuretic and ACE inhibitor therapy to provide maximum benefits

All patients with stable NYHA class II or III heart failure due to left ventricular systolic dysfunction should receive a beta-blocker unless they have a contraindication.

with minimum risks. Generally the contraindications to the use of beta-blockers include sinus node dysfunction, heart rate less than 50 beats per minute, second- or third-degree heart block (without a pacemaker), bronchospastic disease, acutely decompensated heart failure until stabilized and systolic blood pressure less than 100 mmHg. Some of these contraindications are being reevaluated in light of the potential mortality benefits noted above.

Additional large, prospective, double-blind trials are needed to confirm the beneficial effects of beta-blockers on survival in patients with NYHA class IV disease, further define the subset of patients where beta-blocker therapy is contraindicated and establish maximum doses

for selected beta-blockers that best increase rate of survival (Constant, 1998).

The most recently published consensus guidelines on the treatment of heart failure (Packer, 1999) concluded the following:

- All patients with stable NYHA class II or III heart failure due to left ventricular systolic dysfunction (ejection fraction less than 35% to 40%) should receive a beta-blocker unless they have a contraindication or have been shown to be unable to tolerate this treatment; beta-blockers are generally used in combination with diuretics and ACE inhibitors.
- Side effects may occur early in therapy and symptomatic improvement may not be seen until the patient has received treatment for two to three months; however, beta-blockade may reduce the risk of disease progression.
- More data are needed on the effect of beta-blockers in unstable patients and recent NYHA class IV patients.
- Beta-blockers are indicated for the long-term management of chronic heart failure and should not be used in acutely ill patients (rescue therapy) including those who are in the intensive care unit with refractory heart failure requiring intravenous support.
- Abrupt withdrawal of treatment with beta-blockers can lead to dramatic clinical deterioration and should be avoided with a few exceptions.

Search Strategy

The *IDIS* database offers many options for retrieval of primary literature to evaluate the use of beta-blockers in chronic heart failure. Search terms entered in the global field provide a broad overview of the number of articles based on the subject of interest. Entering *heart failure* in the Global field retrieves 54,095 articles within the *IDIS* database. Keep in mind that the Global field searches for either term entered within any field of the records. Therefore this search strategy would retrieve all articles with *heart OR failure* in any field including the cross-index. A search using the *IDIS* controlled vocabulary of valid terms would be more specific. Click on the *Thesaurus* tab to find the *IDIS* valid term and corresponding code number. In the Thesaurus search screen type *heart failure* and press <ENTER> or click on the *Search* button. The disease term for heart failure will be displayed as *FAILURE, HEART, CONGESTIVE 428.0*. Click on the *Main Search* tab to return to the Main Search screen. In the Disease field, type *428.0* (remember that decimal points are part of the *IDIS* number classification system). To include all forms of heart failure, use *428** (utilizing truncation) as your search term. An alternative method to find the valid disease term is to click on the *Phrase* button at the end of the Disease field in the Main Search screen and begin typing the term you are looking

for. In this case the first three letters of the disease term, *fai*, will scroll to a list of terms beginning with these letters, which will include all of the terms for FAILURE, HEART. Next select a term by checking the box beside that term and then click on *OK*. This will insert your selected term into the Disease field of the Main Search screen. This search strategy provides 4,752 records on FAILURE, HEART, CONGESTIVE 428.0.

To limit your search further, combine the drug of interest in the Drug field and FAILURE, HEART, CONGESTIVE 428.0 in the Disease field. In this case, beta-blockers in congestive heart failure are the focus. Click on the *Drug Hierarchy* tab to find the drug and/or pharmacologic class code number and term. In the Drug Hierarchy search screen, type *metoprolol* then click on *Search* or press <ENTER>. You will find the eight-digit code number for metoprolol. If you scroll up or down in this result screen, you can review all of the beta-blockers and you will also see that there is a specific pharmacologic class code number and term: 12160100 BETA-ADRENERGIC BLOCKERS. Then in the Main Search screen you can use either "BETA-ADRENERGIC BLOCKERS" or 12160100 or 121601* (truncate) in the Drug field. Using the first six digits of the code number with truncation will find all articles indexed with either the pharmacologic class term or any of the individual drugs in the class. A search using 428.0 in the disease field and 121601* in the drug field retrieves 473 articles in the *IDIS* database.

The search can be further limited by using the descriptor terms. Click on the *Look Up* icon and scroll through the *IDIS* descriptor list. Then select a term by checking the box beside the term and click on *OK*. If you wish to retrieve articles that include information about the mechanism of action of beta-blockers in heart failure, select the descriptor 41 MECHANISM OF ACTION. Adding 41 in the descriptor field to the search described above retrieves 160 articles.

This article was prepared by Wendi Slaughter and Natalie McFarland, Pharm.D. candidates, the University of Iowa College of Pharmacy.

Kevin Moores, Pharm.D., Assistant Professor (Clinical), the University of Iowa College of Pharmacy, and Director, Iowa Drug Information Network, reviewed the article.

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Accreditation Information



The University of Iowa College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. The ACEP program number is 020-000-99-901-H01. The University of Iowa will award 1 contact hour (0.1 CEU) of continuing pharmacy education for satisfactory completion of this monograph.

To earn continuing education credit, complete the assessment exercise, CE registration form and program evaluation, and return to Iowa Drug Information Service with a processing fee of \$5.00 made out to the College of Pharmacy. A certificate will be awarded upon achieving a passing grade of 70% or better. Pharmacists completing this program by September 1, 2000 can receive credit.

Assessment Questions

Directions

Select the most appropriate answer for each of the following questions and circle the corresponding letter on the answer sheet.

To receive one hour of continuing education credit (0.1 CEU) for successful completion of this program, you must:

1. Complete the answer sheet.
2. Print or type your name, address, social security number and pharmacy license number(s) in the space provided on the CE registration form.
3. Complete the program evaluation.

Mail with processing fee of \$5.00 made out to the College of Pharmacy, your completed answer sheet, registration form and evaluation to:

**Iowa Drug Information Service
ATTN: Donna Brus
The University of Iowa
100 Oakdale Campus N330 OH
Iowa City, IA 52242-5000**

Certificates will be issued to those who score 70% or higher. Those who score below 70% will be notified, and no credit will be recorded. Allow four weeks for processing.

1. Which of the following cardiovascular disorders is currently increasing in prevalence?

- a. atrial fibrillation
- b. heart failure
- c. ischemic heart disease
- d. uncontrolled hypertension
- e. myocardial infarction

2. What is the most frequent cause of hospitalization in persons 65 years of age or greater?

- a. stroke
- b. heart failure
- c. complications of diabetes
- d. myocardial infarction
- e. cancer

3. Which of the following is the oldest form of therapy in chronic heart failure?

- a. beta-blockers
- b. diuretics
- c. angiotensin converting enzyme inhibitors
- d. digitalis
- e. hydralazine

4. The mechanism of the beneficial effect of beta-

blockers in heart failure may include which of the following?

- a. increase in kinin activity
- b. reduced sodium retention
- c. positive inotropic effect
- d. reversal of cardiac remodeling
- e. vasoconstriction

5. Which of the following were demonstrated as an effect of treatment with bisoprolol in the CIBIS-II study?

- a. reduction in the rate of hospitalization
- b. reduced need for diuretic therapy
- c. increase in mortality
- d. reduced need for ACE inhibitor therapy
- e. both a. and c.

6. Carvedilol has been demonstrated in a comparative trial with metoprolol to provide greater reduction in morbidity and mortality in heart failure.

- a. True
- b. False

7. Beta-blockers have been demonstrated in several large, controlled trials to reduce morbidity and mortality in patients with New York Heart

Association (NYHA) Class IV heart failure.

- a. True
- b. False

8. Which of the following would be considered a contraindication to initiation of a beta-blocker in a patient with heart failure?

- a. diabetes
- b. NYHA class II or III heart failure
- c. Third-degree heart block without a pacemaker
- d. Hypertension
- e. Current therapy with a diuretic and an ACE inhibitor

9. Which of the following is true regarding the strategy for starting a beta-blocker in a patient with heart failure?

- a. be prepared to discontinue therapy at the first sign of increased peripheral edema
- b. discontinue diuretic and ACE inhibitor therapy first
- c. educate the patient that side effects may occur initially but improvement may be seen in two to three months and the long-term benefits may include reduced hospitalization and increased length of life
- d. titrate the dose to the maximum recommended within the first week of therapy
- e. only patients with asymptomatic heart failure should be considered candidates

10. Which of the following types of patient would be the best candidate for treatment with a beta-blocker for heart failure?

- a. stable NYHA class II with diuretic and ACE inhibitor therapy
- b. in the intensive care unit needing acute treatment for decompensated failure
- c. NYHA class IV with a systolic blood pressure of 95 mmHg
- d. asymptomatic diastolic heart failure
- e. severe COPD with NYHA class I heart failure

ANSWER SHEET

Circle the most appropriate answer

- | | | | | | | | | | | | |
|----|---|---|---|---|---|-----|---|---|---|---|---|
| 1. | a | b | c | d | e | 6. | a | b | | | |
| 2. | a | b | c | d | e | 7. | a | b | | | |
| 3. | a | b | c | d | e | 8. | a | b | c | d | e |
| 4. | a | b | c | d | e | 9. | a | b | c | d | e |
| 5. | a | b | c | d | e | 10. | a | b | c | d | e |

CE REGISTRATION

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PROGRAM EVALUATION

	Excellent				Poor
Overall quality	5	4	3	2	1
Relevance to practice	5	4	3	2	1
Value of content	5	4	3	2	1
	Agree				Disagree
Important to pharmacists	5	4	3	2	1
Increased my knowledge	5	4	3	2	1
Achieved stated objectives	5	4	3	2	1
Was educational and not promotional	5	4	3	2	1

It took me _____ hours and _____ minutes to read this article and complete the assessment questions.

How to Use the Drug Hierarchy

Located in the tab section (bottom) of the *IDIS* search screen, the drug hierarchy has many benefits for *IDIS* database users. Although use of the hierarchy is not essential for searching the database, it aids users in constructing quicker, more efficient searches. The drug hierarchy is a numeric listing of over 7,000 drug names and their associated drug numbers. These numbers are seven- or eight-digit

modified American Hospital Formulary Service (AHFS) pharmacological-therapeutic classification numbers. Each valid drug term is assigned a seven- or eight-digit code number. The drug's number indicates the drug's pharmacological-therapeutic class.

There are about thirty major pharmacological-therapeutic categories in the *IDIS* drug hierarchy, each containing multiple subclasses. For example, COAGULANTS AND ANTICOAGULANTS is a general category and PLATELET AGGREGATION INHIBITORS is a subclass. The drug hierarchy enables the searcher to (1) obtain the pharmacological-therapeutic classification of a valid drug term or (2) view the terms within a pharmacological-therapeutic class.

This information is useful when you need to obtain the correct pharmacological-therapeutic class number to search for general information about the entire class (for example, DIANOSTIC AGENTS 3600000) or to search, not only one general class term, but also all the individual members of the class (in this example, 36*).

When searchers type a valid drug term into the drug hierarchy search field and click on *Search*, all terms within the hierarchy are displayed. The desired drug term and its numeric code are highlighted within the list. For example, to find the pharmacological-therapeutic class for eptifibatide, type *eptifibatide* into the drug hierarchy search field. 20120649 EPTIFIBATIDE will be highlighted. Scroll up to the first term that ends in "00," in this example, 20120600. Eptifibatide belongs to the sub-subclass 20120600 PLATELET AGGREGATION INHIBITORS, which belongs to subclass 20120000

COAGULANTS AND ANTICOAGULANTS, which in turn belongs to the major category 20000000 BLOOD FORMATION COAGULATION.

Within the pharmacological-therapeutic hierarchy, the lowest category (sub-subcategory) is represented by six digits preceding two 0's, such as 20120600. The subcategory is four digits preceding four 0's (20120000), and the major categories are two digits followed by six 0's (20000000). There are exceptions in the major categories—4000000 ANTIHISTAMINES and 8000000 ANTIINFECTIVES.

Using either the category name or number, such as 20120060, 20120000 or 20000000, in an *IDIS* search will retrieve articles addressing the drug class. A search using the category number truncated, 201206*, 2012*, or 20* will retrieve not only the articles addressing the drug category but also articles for each individual drug within the category.

The drug hierarchy is also a useful tool when the searcher wants to find all drug terms within a pharmacological-therapeutic class. For example, a searcher may want to know what *IDIS* has under cephalosporins. The searcher may not know the exact term the *IDIS* database has for cephalosporins. Therefore, the searcher should use truncation. For example, the searcher should type **cephalosporin** into the drug hierarchy field and click on *Search*. By putting the truncation at the beginning and end of the term, the searcher will be guaranteed to bring up a term with cephalosporin no matter how it is arranged within the term. As a result of this search, ANTIBIOTICS-CEPHALOSPORINS will appear at the top of the screen. The pharmacological-therapeutic class is listed first followed by all the valid drug terms and code numbers in the *IDIS* database for the class. The drugs are listed in order by the drug code numbers and not alphabetically by drug name. Searchers can then scroll down to view all the terms within that class.

The drug hierarchy functions in improving the exploration of the *IDIS* database leading to more efficient searching. Following these basic tips can work to the searcher's advantage.



Jenny Jamison, Pharmacy Intern
Division of Drug Information Service

Perspective from an *IDIS* Subscriber

Re: Withdrawal-type syndrome possibly associated with the discontinuation of paroxetine in a young woman

History of Present Illness

The patient is a 24-year-old female who presented with severe insomnia and fatigue, moderate agitation, dizziness and mild nausea after tapering paroxetine 5 mg to 2.5 mg daily. The patient had been tapering from her original paroxetine dose of 20 mg over the course of four weeks and began experiencing these adverse effects on day 29.

The patient was prescribed paroxetine 20 mg qhs two-and-one-half years ago for a diagnosis of mild depression with severe anxiety. After six weeks of treatment the patient's symptoms of depression and anxiety were significantly better. After two years of treatment the patient's psychiatrist believed she was ready to taper her medication. The patient attempted to taper off the paroxetine in December 1998 and again in March 1999 but was unsuccessful because of unbearable symptoms. Her third (and most recent) attempt occurred in July 1999.

December 1998 taper: The patient tapered from paroxetine 20 mg daily to 10 mg daily for 14 days. She experienced no adverse effects during these 14 days. On day 15 she tapered to 5 mg. That evening she experienced moderate insomnia and night sweats. The following morning she felt moderately fatigued and mildly agitated. The insomnia and night sweats occurred again on the evening of day 16. By day 17 the patient was exhausted and very agitated. Not sleeping was interfering with her college work, so she decided to restart paroxetine 20 mg hs. That evening she experienced only mild insomnia and no night sweats. The morning of day 18 she was less fatigued and had no agitation. That night she slept very well, and by day 19 all symptoms had resolved.

March 1999 taper: The patient again tapered from 20 mg to 10 mg for 14 days without any adverse effects. She planned for the tapering from 10 mg to 5 mg during her spring break, so that the symptoms would not interfere with her college work. On the evening she tapered from 10 mg to 5 mg, she

experienced moderate insomnia and mild night sweats. On day 16 she experienced moderate fatigue, agitation, insomnia and mild night sweats. On day 17 she was moderately fatigued and felt her agitation and irritability to be very severe. This feeling of irritability during her vacation was unbearable. That evening she restarted the paroxetine 20 mg. Her symptoms resolved in the same pattern as in December (by day 19 the patient had returned to baseline).

July 1999 taper: The patient tapered from 20 mg to 10 mg over 21 days. She thought that if she tapered more slowly, it would be easier to complete withdrawal. The patient tapered down to 5 mg on day 21 and continued on this dose for seven days. During this time period she experienced only mild insomnia, night sweats and fatigue. She felt none of these symptoms interfered with daily life. On day 28 she tapered down to 2.5 mg. That evening she

EDITOR'S NOTE: From time to time, we publish articles contributed by *IDIS* subscribers. An article from Dave Mace, B.S.Pharm., is included in this issue. Dave Mace is from an institution that is a long-standing *IDIS* subscriber, utilizing the database on a regular basis. His consult illustrates *IDIS* database use contributing directly to patient care outcomes. The responsibility for errors is the author's alone. The consult does not necessarily represent hospital views and recommendations. We hope you find the information interesting and useful and welcome comments. If you are interested in sharing your experiences using the *IDIS* database, please contact donna-brus@uiowa.edu.



Donna Brus, Editor

experienced severe insomnia (only slept two hours) and mild night sweats. On day 29 she experienced extreme fatigue and dizziness. She described the dizziness as a “buzzed feeling” similar to that of too much alcohol. She felt moderately agitated and mildly nauseous.

Psychiatric Consults

The patient has been consulting with her psychiatrist once every two months for the past two-and-one-half years. He suggested she taper the paroxetine. He advised her to taper it slowly to alleviate possible withdrawal symptoms. Her psychiatrist did not describe the symptoms that might be associated with tapering the paroxetine. She described her unbearable symptoms and her decision to restart the paroxetine 20 mg, which led to resolution of these symptoms. He agreed these symptoms were most likely due to paroxetine withdrawal and advised her to remain on the medication and try to taper again at some later time. In mid-July 1999 she moved from that area and now is no longer able to consult with her psychiatrist.

Literature

Paroxetine

Stahl (1997) reported the symptoms associated with SSRI withdrawal syndrome. Nine hundred forty-seven case reports from the WHO database were reviewed on paroxetine withdrawal. The most frequent symptoms reported included dizziness (142), nausea (63), paresthesia (55), headache (53), vertigo (35), increased sweating (29), agitation (25), tremor (25), fatigue (24) and anxiety (22). Coupland (1996) found similar symptoms when they studied 50 patients experiencing paroxetine withdrawal. The most frequent symptoms included dizziness (16%), movement-related (16%), paresthesia (12%), lethargy (12%), nausea (6%), anxiety (4%), vivid dreams (4%) and insomnia (4%).

Lazowick (1995) reviewed two letters describing patients who experienced paroxetine withdrawal. One letter described five patients who experienced withdrawal symptoms one to three days after tapering off paroxetine. The most common symptom among the five patients was mild to moderate dizziness or lightheadedness. The symptoms resolved in all the patients within four to 14 days. Another letter described a patient who had been treated with paroxetine 10 to 20 mg/d for seven

weeks with a diagnosis of depression and anxiety. Due to an adverse reaction she was switched to fluoxetine 10 mg. After two weeks she experienced anxiety and insomnia, which resulted in switching back to paroxetine for five weeks. Paroxetine was then discontinued because of a hypomanic episode. Three days later the patient complained of nausea, diarrhea, anorexia, chills and incoordination (Lazowick, 1995).

Nine hundred forty-seven case reports from the WHO database were reviewed on paroxetine withdrawal. The most frequent symptoms reported included dizziness, nausea, paresthesia, headache, vertigo, increased sweating, agitation, tremor, fatigue and anxiety.

Barr (1994) studied the efficacy of paroxetine in treating obsessive-compulsive disorder (OCD). During this study three patients received a seven- to 14-day tapering schedule. The following symptoms were reported as a result of tapering: vertigo, gait disturbances, diarrhea, fatigue, myalgia, lightheadedness, rhinorrhea, insomnia, nausea and vomiting.

Fluoxetine

Stahl (1997) reported 271 cases of fluoxetine withdrawal in the WHO database. The most commonly reported symptoms included dizziness (24), nervousness (24), anxiety (21), depression (19), suicide attempt (17), psychotic depression (15), headache (15), convulsions (13), aggressive reaction (9) and agitation (9).

Stoukides (1991) described a 32-year-old male who presented to the emergency room with an acute dystonic reaction. He had been diagnosed with major depression six months earlier and was being treated with fluoxetine. He discontinued the fluoxetine two days before presenting to the ER. The day before he had experienced neck stiffness and that night had woken up with painful extensor muscle spasms and protruding tongue movements. The patient denied any other prescription medications or recreational drug use. A physical exam revealed the following: pulse 100 bpm, blood pressure 180/100, tremor and prominent muscle movements. Laboratory data was within normal limits (WNL) and a toxicology screen was negative. The patient was treated with 50 mg IM

diphenhydramine, and complete resolution of symptoms occurred over 45 minutes.

Sertraline

Stahl (1997) also reported 170 cases of sertraline withdrawal. The most frequently reported symptoms included dizziness (142), nausea (63), paresthesia (55), headache (53), vertigo (35), increased sweating (29), agitation (25), tremor (25), fatigue (24) and anxiety (22). Coupland (1996) reported 45 cases of sertraline withdrawal in whom the only symptom was dizziness in one patient (the remainder were asymptomatic).

Wolfe (1997) described a 43-year-old male treated for depression with sertraline 25 mg/d for about six months. The patient experienced drowsiness on this regimen, and the dose was decreased to 12.5 mg for a week and then discontinued. Venlafaxine, 37.5 mg, one-half tablet twice a day was begun. Forty-eight hours later, the patient experienced severe dizziness and lightheadedness that was worsened by changes in position, but without a feeling of spinning or nausea. Five days later venlafaxine was discontinued. After the dizziness persisted for another week, sertraline 12.5 mg was restarted and the symptoms resolved by the following day. Later he tapered slowly off the sertraline without any report of symptoms.

Lazowick (1995) described a 46-year-old woman who was titrated over four weeks to sertraline 150 mg/d. The dosage was then decreased to 100 mg/d and then abruptly discontinued five weeks later. Two days later the patient experienced fatigue, severe abdominal cramps, stomach distension, insomnia, impaired memory and flu-like symptoms. Sertraline 25 mg was restarted and the symptoms quickly disappeared. The authors also described a 22-year-old male receiving sertraline 150 mg/d that was tapered by 50 mg every 10 to 20 days over eight weeks. The patient experienced electric shock-like sensations that lasted one second every five to 10 minutes. The shock-like symptoms decreased in intensity over one month and then disappeared 13 weeks after sertraline therapy was discontinued.

Fluvoxamine

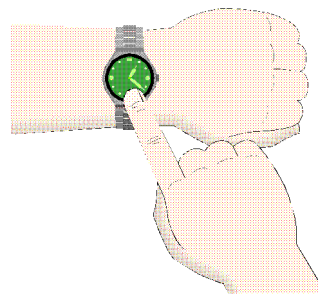
Coupland (1996) reported 43 cases of fluvoxamine withdrawal. The reported symptoms included dizziness (9%), paresthesia (2%), lethargy (4%), nausea (7%), lowered mood (7%), anxiety (2%), vivid dreams (7%), insomnia (2%), headache (7%), irritability (4%) and movement-related (7%).

Lazowick (1995) described a 30-year-old woman with OCD who had been taking fluvoxamine 100 mg/d. She tried to discontinue the medication upon

Continued on page 12

Time to Renew

Renewal materials for the 2000 *IDIS* database subscription were mailed in early September. We ask that you respond as soon as possible. Your current subscription will expire after the December 1999 update. To avoid interruption of service, your renewal must be received by January 12, 2000. In the event you misplace or fail to receive a renewal form, please contact our office as soon as possible. Thank you for your attention to your 2000 renewal.



becoming pregnant. She experienced such severe aggression with its withdrawal, however, that she continued the medicine throughout her pregnancy. Mallya (1993) described four patients who reported withdrawal symptoms after tapering from fluvoxamine. All four patients experienced dizziness, and two patients experienced stomach pain, fatigue, memory problems and confusion. One patient restarted fluvoxamine therapy with remission of symptoms, and the other three patients' symptoms remitted within several weeks.

Black (1993) studied the abrupt discontinuation of fluvoxamine in 13 patients with panic disorder after eight months of treatment. All the patients experienced symptoms, the most frequent of which occurred on day five and included dizziness, incoordination, headache, irritability and nausea. Symptoms had disappeared in all patients by day 14. This study showed a short-lived withdrawal syndrome associated with abrupt discontinuation of fluvoxamine.

Comment

The patient has experienced a similar syndrome each time she tried to taper off paroxetine 20 mg. The first two episodes occurred over the same time period (16 days) and had very similar presentations,

Differences among the SSRIs in the frequency and intensity of withdrawal syndromes seem to correlate with the drug's individual pharmacokinetic profile.

the only difference being milder night sweats with the second taper. The third episode occurred over a longer time period, which led to milder symptoms on the 5-mg dose. When she tapered down to 2.5 mg, however, the symptoms were severe.

Differences among the selective serotonin reuptake inhibitors (SSRIs) in the frequency and intensity of withdrawal syndromes seem to correlate with the drug's individual pharmacokinetic profile. The short half-life SSRIs (paroxetine has the shortest half-life of all the SSRIs) are more commonly associated with acute and more severe discontinuation symptoms (Zajecka, 1997). Wolfe (1997) described a retrospective study with 21 cases of withdrawal reactions that had the following incidence rates: paroxetine 20%, fluvoxamine 14%, sertraline 2.2%

and fluoxetine 0%. Wolfe also included data from a review of adverse reactions that showed the incidence of withdrawal reactions to be higher with paroxetine (0.3 reports per 100 prescriptions) than

To avoid severe paroxetine withdrawal, it is recommended that abrupt discontinuation be avoided and doses tapered over time.

with sertraline and fluvoxamine (0.03) and least with fluoxetine (0.002). Based on this data, the withdrawal reaction rates were 35% with paroxetine, 3% to 4% with sertraline and fluvoxamine and 0.05% with fluoxetine.

To avoid severe paroxetine withdrawal, it is recommended that abrupt discontinuation be avoided and doses tapered over time. If discontinuation symptoms surface during the course of an SSRI taper, the rate of taper should be decreased (Zajecka, 1997). There is no defined treatment of paroxetine withdrawal. Some authors suggest using fluoxetine as a treatment because it relieves the symptoms of withdrawal and then can be tapered off with a lower incidence of adverse reactions (Dominguez, 1995; Coupland, 1996). Wolfe however claims that substituting a different antidepressant is unreliable and should only be done to treat the underlying psychiatric illness. The only way to alleviate the symptoms is to restart the paroxetine. Studies have shown that the symptoms of paroxetine withdrawal disappear within 24 to 48 hours after restarting the medication (Wolfe, 1997).

Follow-Up

The afternoon of day 29 the patient decided to once again restart her paroxetine 20 mg. She felt too miserable to be able to function in her daily activities. Two hours after restarting, her dizziness and agitation had remitted. That evening she slept only four hours despite the use of diphenhydramine 50 mg and an additional paroxetine 20 mg at 2 a.m. On day 30 the patient felt moderately fatigued and felt a loss of appetite. That evening she had mild insomnia. By day 31 all the symptoms had resolved. The patient continued on paroxetine 20 mg for two more weeks. On week 3 she tapered down to 10 mg daily with no incidence of adverse effects. Her plan is to continue on 10 mg daily for six months with the intent of establishing a convenient time to taper and discontinue paroxetine.

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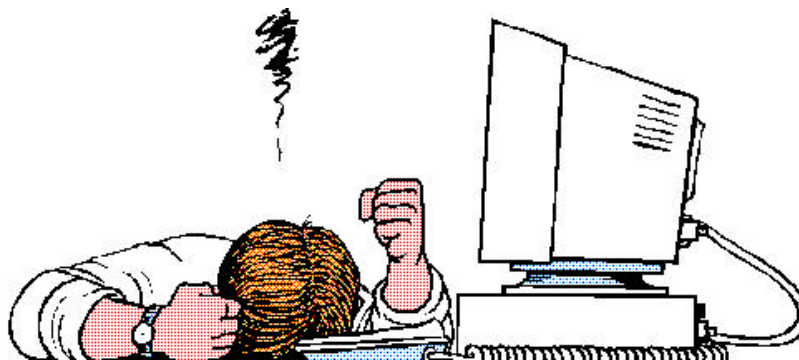
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This article was prepared by Elizabeth Bretz, Pharm.D. candidate.

Dave Mace, R.Ph., Drug Information Specialist, reviewed the article. Mace graduated from the University of Iowa College of Pharmacy in 1967. Since 1982 he has served as the Director of the Drug Information Center at BPVAMC, 10,000 Bay Pines Blvd., Bay Pines, FL 33744. His responsibilities include serving as a preceptor for drug information and Pharm.D. clerkship programs and responding to complex drug information requests from clinical staff.

Y2K: No Need to Worry

IDIS System/CD-ROM is Year 2000 compliant. The publication year is the only date field in the database and is currently in four-digit format. There is no code in the retrieval software which is affected by the system date. Please contact us if you need additional information.



FDA DRUG/BIOLOGIC APPROVALS

Generic Name (FDA Therapeutic Classification) <i>Trade Name</i>	Sponsor (Approval Date)	Valid IDIS Drug Term Drug Number (<i>IDIS Citations</i>)*	Indication/Use	Valid <i>IDIS</i> Disease Term Modified ICD-9-CM Number
Ganirelix Acetate (1P)** <i>Antagon</i>	Organon (July 29)	GANIRELIX 68180903 (3 citations)	Provides for the inhibition of premature LH surges in women undergoing controlled ovarian hyperstimulation	Dysfunction, Ovarian NEC 256. Prophylaxis NEC V07.
Ketotifen Fumarate (1P) <i>Zaditor</i>	Ciba Vision (July 2)	KETOTIFEN 4000021 (274 citations)	Antihistamine for the temporary prevention of itching of the eye due to allergic conjunctivitis	Conjunctivitis, Acute 372.0 Prophylaxis NEC V07.
Pioglitazone (1P) <i>Actos</i>	Eli Lilly (July 15)	PIOGLITAZONE 68200417 (2 citations)	Treatment of type II diabetes or adult onset diabetes	Diabetes Mellitus 250.
Rofecoxib (1P) <i>Vioxx</i>	Merck (May 20)	ROFECOXIB 28080602 (12 citations)	COX-2 inhibitor for once-daily use in the relief of signs and symptoms of osteoarthritis, management of acute pain in adults and treatment of menstrual pain	Osteoarthritis 715. Pain NEC 782.2 Dysmenorrhea 625.3
Rosiglitazone (1P) <i>Avandia</i>	SmithKline Beecham (May 25)	ROSIGLITAZONE 68200418 (3 citations)	For use as adjunct to diet and exercise to improve glycemic control in patients with type II diabetes mellitus as monotherapy or in combination with metformin	Diabetes Mellitus 250.
Zanamivir (1P) <i>Relenza</i>	Glaxo Wellcome (July 26)	ZANAMIVIR 8180096 (18 citations)	Treatment of uncomplicated influenza virus in adults and adolescents aged 12 years and older. Approved to treat both types A and B influenza	Influenza 487.

* Through August 1999 Update. Complete bibliographic citations will be provided upon request.

** (1P) New Molecular Entity given priority review by FDA

KEY
REFERENCES

New Drug Selected Bibliography

This new drug selected bibliography provides a selection of key clinical studies and reviews of new drugs approved by the FDA.

IDIS SYSTEM/CD-ROM was searched to retrieve key articles relevant to the new drug **zanamivir** and its approved uses.

Monto AS, Robinson DP, Herlocher ML et al. Zanamivir in the prevention of influenza among healthy adults: a randomized controlled trial. *JAMA*. 1999;282:31-35. (*IDIS* Article Number 427990). *At two sites, investigators conducted a randomized, double-blind, placebo-controlled trial in 1,107 healthy adults, 18 to 69 years old, to assess the efficacy of 10 mg zanamivir, administered once daily by oral inhalation.*

Campion K, Silagy C, Keene O et al. Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. *Lancet*. 1998;352:1877-1881. (*IDIS* Article Number 418344). *A report of the MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group on a multicenter, randomized, double-blind, placebo-controlled phase III trial that was conducted to assess efficacy and safety of 10 mg of inhaled zanamivir in 455 healthy individuals aged 12 years or older.*

Hayden FG, Osterhaus AD, Treanor JJ et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza virus infections. *N Engl J Med*. 1997;337:874-880. (*IDIS* Article Number 391783). *A report of two separate multicenter, randomized, double-blind studies conducted in North America and Europe in which investigators assessed the therapeutic activity of zanamivir 6.4 mg by intranasal spray plus 10 mg by inhalation, zanamivir 10 mg by inhalation plus placebo spray, or placebo by both routes twice daily for five days in 262 adults with influenza-like illness of less than 48 hours' duration.*

To date, it appears that there are no published studies that evaluate the efficacy of **ketotifen fumerate ophthalmic solution** for the temporary relief of itching of the eye due to allergic conjunctivitis. However, during the new drug approval process, a Summary Basis of Approval (an official United States Food and Drug Administration [FDA] document) is compiled for each new drug being reviewed. This document includes summaries of the pivotal and supportive clinical studies conducted during the approval process. These studies are often not published elsewhere. Following the FDA approval of a new drug, these documents are requested from the FDA and are then indexed and included as part of the *IDIS* database. Use descriptor 155 SUMMARY BASIS OF APPROVAL in combination with the valid drug term to retrieve these documents from the database.



Ruth Calloway, R.Ph., M.S.

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Annual Meeting
Kansas City, Kansas
October 24-27

American Society of Health-System Pharmacists (ASHP)
Midyear Clinical Meeting
Orlando, Florida
December 5-9



STAFF PROFILE

Tracy Simenson joined the *IDIS* staff as a Clerk Typist II in November of 1998. Her duties include processing orders in the accounting office and providing assistance for DDIS subscribers. In addition, with a B.S. in journalism from the University of Iowa, Tracy is the Assistant Editor of the quarterly newsletter.

Before she started at *IDIS*, Tracy toured Germany and France exploring medieval castles, visiting quaint little villages and dining at the finest bistros. Her favorite part of the whole trip was overcoming her fear of fast cars and driving on the autobahn.

In her spare time she enjoys attending theatre and opera, reading a good book, spending time with her family and going out with her friends.

Tracy Simenson

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Editor.....Donna Brus
Assistant Editor..... Tracy Simenson
Production/Design CoordinatorJane Heaton
Photographer..... David Luck



Iowa Drug Information Service

Telephone: 319-335-4800
U.S. Toll-Free: 800-525-IDIS
Fax: 319-335-4440
E-mail: IDIS@uiowa.edu
Web Site: <http://www.uiowa.edu/~idis>



Iowa Drug Information Network

Telephone: 319-335-4199
U.S. Toll-Free: 800-791-7055
Fax: 319-335-4440
E-mail: IDIN@uiowa.edu
Web Site: <http://idin.idis.uiowa.edu>

Division of Drug Information Service
The University of Iowa, 100 Oakdale Campus N330 OH
Iowa City, IA 52242-5000 USA