

# World of Drug Information

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CURRENT CLINICAL  
ISSUES

## Antidepressant Therapy for Late Onset Depression

Goal: To increase awareness of the appropriate use of antidepressants in geriatric patients with late onset depression.

### Learning Objectives:

1. Explain the risk factors and diagnostic challenges of late onset depression.
2. Discuss the side effects of the monoamine oxidase inhibitors and second generation antidepressants pertinent to the geriatric population.
3. Discuss the advantages and disadvantages of the various classes of antidepressants in geriatric patients.
4. Describe the dosing considerations of antidepressants in elderly patients.
5. Explain the role of the pharmacist in counseling elderly patients treated with antidepressants.

Late onset depression is becoming a significant health care problem as life expectancy increases worldwide. According to World Health Organization (WHO) projections within the next twenty-five years the worldwide average life expectancy will be fifty years old and 10 percent of the population will be over 65 years old. (WHO, 1998) Healthcare providers need to become aware of the issues regarding depression in the elderly and respond to the special treatment challenges they present. The prevalence of depressive symptoms is estimated at 15 percent of community residents over 65 years old (Friedhoff, 1992), but major depression among the elderly in the community is estimated to be less than 3 percent and 15-25 percent in nursing homes. These estimates are based on data collected from the Epidemiology Catchment Area Study. (Nelson, 1998) The estimates may vary due to the source of the sample, definition of depression or the

assessment method and the experience of the rater.

Unfortunately, depression in the elderly is under-diagnosed and under-treated, because the patient or the healthcare provider may inaccurately attribute symptoms to the patient's reaction to the many physical, economic, or

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psychosocial changes that occur during the aging process. Depression is not a natural part of the aging process. By one estimate, only 10 percent of the elderly who need treatment receive it. (Friedhoff, 1992)

The diagnosis and treatment of late onset depression in the elderly presents unique challenges to clinicians. Depression in the elderly does not always exhibit as the depressed mood seen in younger patients. Older patients are more likely to exhibit vegetative symptoms such as loss of appetite or refusal to eat, sleeplessness, somatic complaints including anergia, loss of interest and enjoyment of normal activities and cognitive dysfunction (difficulty concentrating, apathy). (Reynolds, 1996) The other diagnostic challenges related directly to the patient are: hesitance of the patient to mention his or her symptoms due to a lack of understanding of the aging process, concern with the stigma attached to mental illness, attributing the symptoms to coexisting conditions or side effects of the medications used to treat these conditions, or the fear that the healthcare provider will not listen to his or her concerns. (Friedhoff, 1992) Late onset depression is differentiated from major depression in the elderly because it starts when the patient is over 65 years old rather than being a continuation of depression already present and then remaining into advanced age.

The Geriatric Depression scale or the Beck Depression Inventory is used for assessment. A score greater than 10 using either assessment tool requires further evaluation. The symptoms must be present every day during the two week screening period and show a change from the previous functioning level. (Reynolds, 1996) Clinicians need to be especially vigilant in patients with the following risk factors: female gender, lack of social support, family history of depression, chronic medical illnesses, specific drug therapies, alcohol abuse or a stressful life. (Friedhoff, 1992) Major depression is not a normal consequence of medical illness or bereavement, but depressive symptoms are a natural reaction to those experiences. If the symptoms persist for two months after a loss or medical condition change, the patient should be

monitored and depression assessment should be considered. The diagnosis of depression can be further complicated by the frequency of co-existing dementia. Both diseases can present with similar symptoms, but the time progression differs. Depression symptoms develop over weeks, in contrast to years for dementia. In dementia, mild dysphoria or apathy is common and severe persistent dysphoria indicates depression. (Nelson, 2001)

The goal of treatment of late onset depression in the elderly should be to improve the patient's quality of life in the context of treating the whole person. Nonpharmacological therapies including psychotherapy, light therapy and electroconvulsive therapy, may be necessary for optimal treatment of select patients. Nonpharmacological therapies will not be discussed in this article. This article will focus on the use of antidepressants in the treatment of late onset depression in the elderly.

There is no single antidepressant of choice in the elderly patient based only on clinical efficacy. The clinical efficacy of any single agent is between 50 and 65 percent in geriatric patients, which is similar to the rates in younger patients. (Gerson, 1988) Selection of the antidepressant should consider the age-related physiological changes and co-morbid conditions that may affect the drugs pharmacokinetics, pharmacodynamics and alter sensitivity to the drug or affect potential side effects. (Semla, 1998) The armamentarium of agents to treat depression includes monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and other second generation antidepressants.

Monoamine oxidase inhibitors have been shown to be effective in the treatment of late onset depression, but are rarely used in the elderly due to their common side effect of orthostatic hypotension. (Georgotas, 1989) Orthostatic hypotension is a very serious side effect in geriatric patients, due to the gait disturbances and potential for falls and bone fractures in the frail elderly. The MAOIs are also associated with drug interactions with foods high in

tyramine leading to the potential for a hypertensive crisis. (Nelson, 2001)

Tricyclic antidepressants were the mainstay of treatment of depression in the elderly for many years. TCAs are effective even in the very old patients (75 years and older). Few studies have been done in the very elderly, but Katz and colleagues studied the efficacy and pharmacokinetics of nortriptyline in 24 very elderly patients (mean age 84 years old) living in an institutional setting. Nortriptyline was effective in this population and they found no difference in the pharmacokinetics in the elderly versus younger patients. (Katz, 1990)

Although TCAs are effective in treatment of late onset depression, they are no longer considered first line therapy due to their side effects and potential lethality in an overdose. (Nemeroff, 1994) The elderly patient's altered renal excretion ability delays the elimination of the hydroxy metabolites of TCAs and can affect the cardiovascular system, causing delayed ventricular conduction and an increased heart rate (8-10 beats per minute). (Salzman, 1999) In patients with co-morbid heart disease TCAs can lower the threshold for bundle branch block, complete heart block or sudden death. TCAs also block the alpha adrenergic receptors resulting in orthostatic hypotension and increase the risk of falls and bone fractures. (Flint, 1997; Glassman, 1993). TCAs block the central and peripheral cholinergic receptor, causing dry mouth, blurred vision, constipation, urinary retention or hesitancy and cognitive impairment. They also block the histaminergic receptors which results in sedation. The secondary amines, desipramine and nortriptyline, have fewer anticholinergic effects, fewer cardiovascular effects and are less sedating compared to imipramine and amitriptyline. (Richelson E, 1990)

Among the possible antidepressant treatment options many clinicians consider the serotonin selective inhibitors first line agents in elderly patients. (Devane, 1992; Dunner, 1992). The SSRIs efficacy is similar to the TCAs. (Dunner, 1994). The SSRIs have the advantage of a better side effect profile. They exhibit only

weak or absent cholinergic toxicity, lack sedative effects and are less lethal in an overdose. (Preskorn, 1993; Pollock, 1998) SSRIs exhibit a mild decrease in heart rate, but conduction and blood pressure is not affected. Nelson and colleagues conducted a six week randomized double blind study comparing nortriptyline (given at a dose to maintain a plasma concentration of 50-150 ng/ml) with paroxetine (20-30 mg/day) in 81 patients with major depression and ischemic heart disease. Both paroxetine and nortriptyline were efficacious with response rates of 66 percent and 73 percent improvement respectively based on the Hamilton scale. Paroxetine was better tolerated than nortriptyline with less treatment discontinuation (10 percent versus 35 percent respectively). The rate of cardiovascular events leading to discontinuation was significantly higher in paroxetine vs. nortriptyline. (Nelson, 1999)

The most common side effects of the SSRIs are gastrointestinal disturbances and headaches which can be minimized by slow dose escalation. The side effect profiles for most SSRIs are similar if compared at equivalent doses. Most side effects are related to the mechanism of increased availability of serotonin. Fluoxetine is associated with a higher incidence of anxiety. This can be alleviated by administering the drug in the morning. (Reynolds, 1996) Sertraline is associated with diarrhea, which is minimized by gradual dose titration. (Grimsley, 1992). A study done by Pollock and colleagues compared the serum anticholinergic activity of paroxetine (n=31) and nortriptyline (n=30) and found paroxetine has one-fifth the anticholinergic potential of nortriptyline at therapeutic concentrations in elderly patients. (Pollock, 1998)

Hyponatremia, weight loss and gait disturbances are especially important side effects in the elderly and require careful monitoring. When Liu and colleagues reviewed reports of drug-induced hyponatremia and the syndrome of inappropriate secretion of antidiuretic hormone, they found 736 cases of hyponatremia in patients on SSRIs. Seventy-five percent of the

cases were in patients over 65 years old. (Liu, 1996) Elderly patients commonly experience side effects during initial therapy. Studies have noted considerable weight loss during acute treatment with fluoxetine. (Brymer, 1992; Robinson, 2000) A comparison study found more weight loss with fluoxetine versus sertraline, although the difference in weight was not large (-3.2 lbs versus - 1.7 lbs respectively,  $p=0.018$ ). (Newhouse, 2000)

In a recent study, Bondareff found that SSRIs are more likely than TCAs to improve cognition in elderly depressed patients. In a double blind parallel design 12 week study comparing nortriptyline with sertraline in 210 outpatients over 60 years old, the results showed improved cognition in sertraline patients. Nortriptyline patients showed less improvement or had cognitive decline. Patients on sertraline also had improved energy levels and quality of life. (Bondareff, 2000)

Differences between the SSRIs are related to their elimination half-life and drug-drug interactions. Dosing in the elderly must be done cautiously and slowly. It is prudent to start with a low dose and check tolerance to side effects. Older patients may take longer to respond to drug therapy compared to younger patients. (Bondareff, 2000)

Fluoxetine has an elimination half life of 2-3 days for the parent compound and 5 days for the metabolite. (Nelson, 2001) Patients taking fluoxetine do not have withdrawal symptoms if a dose is missed. The other SSRIs have shorter elimination half-lives and are dosed on a once daily basis, which increases patient compliance. (Nelson, 2001) Fluoxetine and paroxetine are both usually started at 10 mg daily and titrated to an effective dose of 20-40mg daily. Sertraline should be started at 25-50mg/day and slowly titrated up to avoid the gastrointestinal side effects. (Reynolds, 1996). The patient should be told not to expect a response to antidepressant therapy for at least 4-8 weeks. The drug should be continued for 6-9 months after remission of the first episode and at least one year after a second or third episode. (Stokes, 1993)

Drug-drug interactions are an important part of antidepressant drug selection. Paroxetine and fluoxetine are potent inhibitors of the CYP2D6 pathway. Fluoxetine also affects the CYP2C9 pathway. Fluvoxamine is a potent inhibitor of CYP1A2. (Reynolds, 1996) These metabolic pathway inhibitions can have important drug-drug interaction consequences. Most elderly patients are on multiple medications making concurrent medications an important factor for antidepressant selection.

The second generation antidepressants, bupropion, venlafaxine, nefazodone, and mirtazapine, have proven to be efficacious in the treatment of depression in the elderly. (Mahapatra, 1997; Weihs, 2000; Fava, 2001; Nelson, 2001) When treating the elderly, new antidepressants' potential advantages need to be weighed against the cost, side effects, efficacy and ease of dosing regimen to improve compliance. The cost of the new generation of antidepressants is a definite disadvantage for patients on a fixed income. Bupropion is a norepinephrine reuptake blocker. It lacks anticholinergic side effects and does not cause orthostatic hypotension, but it has been shown to put patients at a greater risk of seizures compared to other agents. (Salzman, 1999). Also, it requires twice a day dosing which often affects patient compliance. Venlafaxine is similar to the TCAs in pharmacological properties, but lacks anticholinergic side effects. It can cause headaches and nausea. Thase and colleagues, 1998, in a meta-analysis on the effects of venlafaxine on supine diastolic blood pressure, found a dose-dependent effect. The incidence of elevated diastolic blood pressure was three times greater among patients treated with more than 300 mg/day compared to those treated with lower doses during initial therapy. Nefazodone, a serotonin antagonist, has no sexual side effects and has a beneficial affect on sleep, but it is sedating and requires twice daily dosing. It is also a potent inhibitor of the CYP3A4 metabolic pathway. (Nelson, 2001) Mirtazapine is an alpha antagonist and has beneficial effects on sleep, weight maintenance and has no significant drug-drug interactions. It may cause

daytime sedation and requires dose titration. (Nelson, 2001)

The pharmacist plays a key role in the treatment of depression in the elderly. Pharmacists have a responsibility to educate patients and increase community awareness about depression and antidepressant drugs. The pharmacist also needs to educate patients receiving antidepressant therapy that it may take 2-8 weeks before they see a response, alert them to potential side effects and encourage medication compliance. Potential drug-drug interactions require vigilance because patients may be taking multiple medications for concurrent medical conditions.

The aging population worldwide presents new healthcare challenges. The entire healthcare team needs to be involved to help the elderly maintain a good quality of life. Depression is not just a part of aging, but instead is a separate disease state that can be treated to improve a patient's quality of life.

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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 ACPE program number is 020-000-02-019-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 Division of Drug Information Service with a \$5.00 check for the processing fee, made out to the College of Pharmacy. A certificate will be awarded upon achieving a passing grade of 70% or better. Pharmacists must complete this program by July 1, 2003 to receive credit.

### \*\*\* ERRATUM \*\*\*

An error occurred in an article that appeared in the March 2002 issue. In the "Unit Dose Drug Distribution" article on Page 14, William W. Tester was incorrectly identified under his picture as William R. Tester. The error has been corrected in the Volume 13, Issue 1 – March 2002 newsletter found on the IDIS Web site (<http://www.uiowa.edu/~idis>). We regret this error.



Mary Ann Cull is a 1989 graduate of the University of Iowa College of Pharmacy (B.S.Ph.). Since that time she has been a pharmacist in the College of Pharmacy's Division of Drug Information Service. Mary Ann's responsibilities include indexing articles for the

IDIS database, overseeing the access and evaluation of print and electronic journals for the Division and contributing articles for the *World of Drug Information* newsletter.

## Announcing Two New Descriptors

Two new descriptors have been added to the IDIS database with the May Update. Both of these new descriptors have been applied retrospectively to articles already in the database.

### 160 ADM IRRIGATION

Definition:

Absorption of a drug through internal or external washing of a body cavity, surface or wound by flowing solution that is then removed.

This descriptor has been added to the Descriptor List under the category THERAPEUTIC, and under the subcategory ADMINISTRATION. When possible, 160 ADM IRRIGATION will be used in conjunction with other descriptors, such as 124 ADM EYE or 65 ADM TOPICAL, to construct more specific search strategies.

### 161 SYSTEMATIC REVIEW

Definition:

A quantitative or qualitative review that synthesizes the results of multiple primary investigations addressing a focused clinical topic. A comprehensive literature search strategy is used to locate all applicable data. Selection of studies to be included is based on uniformly applied criteria and rigorous critical appraisal of each study.

This new descriptor will appear on the Descriptor List under ARTICLE CLASSIFICATION, DESIGN/ANALYSIS and will be used in conjunction with any of the appropriate REVIEW descriptors. Quantitative systematic reviews will also be tagged with the descriptor 145 META-ANALYSIS.



Nicola Sarrazin, R.Ph., Pharm.D.

## Assessment Questions

- The risk factors for late onset depression include all of the following **EXCEPT**?
  - lack of social support
  - male gender
  - family history of depression
  - stressful life
- Why are monoamine oxidase inhibitors rarely used in late onset depression?
  - high cost of the drugs
  - monoamine oxidase inhibitors are commonly associated with a drug-food interaction with foods high in tryptophan
  - orthostatic hypotension is a common side effect
  - monoamine oxidase inhibitors can cause severe respiratory distress
- According to Stokes dosing recommendations, patients on SSRIs should be treated for how long after remission for a first episode?
  - 2-4 weeks
  - 6-8 weeks
  - 1-2 months
  - 6-9 months
- Which of the following statements about the second generation antidepressants is **correct**?
  - Bupropion is an alpha agonist which has beneficial effects on sleep
  - Venlafaxine has strong anticholinergic side effects
  - Nefazadone lacks sedative side effects and can be dosed once daily
  - Mirtazine is an alpha antagonist and has beneficial effects on sleep
- Which is **NOT** a cardiovascular side effect of the tricyclic antidepressants?
  - decreased heart rate
  - increased heart rate
  - delayed ventricular conduction
  - lowering the threshold of bundle branch block
- What are the most common side effects of the SSRIs?
  - sedation and cognitive impairment
  - gastrointestinal disturbances and headaches
  - respiratory and urogenital dysfunctions
  - seizures and nerve palsy

## Directions

Select the most appropriate answer for each of the following questions and **circle the corresponding letter on the answer sheet (Page 8)**.

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

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

**Mail a \$5.00 check made out to the College of Pharmacy, your completed answer sheet/registration form/evaluation to:**

**Division of 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. Please allow four weeks for processing.

- The recommended initial dose of fluoxetine to treat late onset depression is?
  - 10 mg QD
  - 10 mg BID
  - 50mg QD
  - 50 mg BID
- Which antidepressant is associated with a higher incidence of anxiety compared to other SSRIs?
  - sertraline
  - fluvoxamine
  - fluoxetine
  - nortriptyline
- Which of the following is **NOT** a challenge in diagnosing late onset depression?
  - hesitance of the patient to mention his/her symptoms
  - patient is concerned about a stigma attached with depression
  - major depression is just a natural part of aging
  - depression and dementia have similar symptomatic presentations
- In which of the following areas does the pharmacist have a role in helping patients with late onset depression?
  - patient education and drug-drug interactions awareness
  - initial antidepressant drug selection
  - administering the Geriatric Depression scale and depression diagnosis
  - reassuring the patient that major depression is just a natural part of aging

# ANSWER SHEET

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

## CE REGISTRATION

(please print)

ACPE Program #020-000-02-019-H01

Title of Educational Activity (Article) Antidepressant Therapy for Late Onset Depression

Name \_\_\_\_\_

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\*The University of Iowa College of Pharmacy requests this information for the purpose of processing your registration. No persons outside The University of Iowa College of Pharmacy are routinely provided this information.

I hereby certify that I have taken this test:

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

## 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.

# Retrieving Best Evidence with New Descriptor SYSTEMATIC REVIEW 161

The addition of a new descriptor for systematic reviews will facilitate retrieval of reviews containing the best evidence on focused clinical topics. This descriptor is applied to both quantitative and qualitative systematic reviews, and will be used in conjunction with the appropriate review term to designate the age group or groups addressed in the article. Quantitative systematic reviews are also indexed with the descriptor META-ANALYSIS 145.

To find all systematic reviews on a particular disease topic, enter the valid disease term into the Disease Field and descriptor “SYSTEMATIC REVIEW 161” into the Descriptor Field of the Advanced Search screen. This search will retrieve both quantitative as well as qualitative reviews for all age groups.

There are two methods to retrieve age specific systematic reviews; one method is more specific than the other. For the less specific method, simply enter the valid descriptor terms for systematic review along with the review descriptors of interest into the Descriptor Field. For instance, to find systematic reviews that include geriatric populations, enter “SYSTEMATIC REVIEW 161” and “REVIEW GERIATRIC 23”. This will retrieve articles that include geriatric populations, but may not be focused on that group.

Other disease population age tags are FETUS V28., NEONATE V39., PEDIATRIC V85., and PUBERTY AND ADOLESCENCE V21.1. To retrieve systematic reviews that focus on the geriatric population, enter a disease population age tag, such as “GERIATRIC V86.”, into the Disease Field, and enter the term “SYSTEMATIC REVIEW 161” into the Descriptor Field. Articles retrieved by this method may contain other age groups, but the focus will be on the geriatric population.

It is also possible to select systematic reviews that include only quantitative reviews or only qualitative reviews. For quantitative reviews only, enter “SYSTEMATIC REVIEW 161” AND “META-ANALYSIS 145” into the Descriptor Field of the Advanced Search screen. To retrieve only qualitative systematic reviews, enter “SYSTEMATIC REVIEW 161” AND NOT “META-ANALYSIS 145” into the Descriptor Field.

These descriptor terms can easily be selected by using the LOOK UP button located beside the Descriptor Field. Use of this new descriptor for systematic reviews will help ensure retrieval of the best review articles for specific topics.



Nicola Sarrazin, R.Ph., Pharm.D.

# Perspective from an *IDIS* Subscriber



Re: Treatment of possible dementia or depression with thyroxine in an elderly patient with an elevated TSH and low free T4. What are the chances for long term improvement in her mental status?

## Data:

The patient is a 77 year-old white female, she is alert and oriented with some confusion about detailed questions. She was admitted to the GEM (Geriatric Evaluation & Management) unit on March 21, 2002. VITALS – pulse 78, respiratory rate 20, temperature 99.7, blood pressure 145/71.

## Chief Complaint:

Recent problems with self catheterization resulted in urinary retention and catheter placement during clinic visit leading to admission.

## History of Present Illness:

The patient has been living alone under the supervision of her two sons and was followed by our hospital based primary care service. She had been at her usual level of function until the death of her spouse which occurred between one and two years prior to admission. She had been admitted to acute medicine service twice within the past year once for melena and gastrointestinal (GI) bleed and once for falls and generalized weakness. During the most recent admission her mental status had improved after three to four days of intravenous therapy, control of her blood sugar, and treatment of a urinary tract infection. She is now admitted to GEM because of inability to care for herself at home, including problems with blood sugar control, malnutrition, dehydration, medication compliance, and self catheterization.

## Past Medical History:

Alcoholic cirrhosis of the liver with esophageal varices and gastropathy, diabetes mellitus (15 years – on insulin), status post (s/p) GI bleed, anemia, coronary artery disease (CAD), s/p coronary artery bypass graft (CABG), history of transient ischemic attacks (10 years ago), neurogenic bladder with urinary retention,

recurrent urinary tract infections (UTI's), s/p hysterectomy due to history of cervical and uterine cancer, dementia, depression, no alcohol past twenty years, no nicotine past 10 years, no history of previous treatment for hyperthyroidism or family history of thyroid disease.

## Database:

On 3/21/2002 unless other date specified: 169 lbs, 67 inches, (blood urea nitrogen) BUN/s, creatinine 13/0.8 mg/dl, sodium 140 mEq/L, potassium 3.4 mEq/L, liver function tests all within reference range except alkaline phosphatase 150 U/L, HATTS nonreactive, syphilis serology nonreactive, iron 20 ug/dl, % saturation 6.1%, ferritin 19.3 ng/ml, folic acid 13.6 ng/ml, vitamin B 12 1356 pg/ml, thyroid stimulating hormone (TSH) 10.89, (thyroglobulin and thyroid peroxidase antibodies not available), Free T4 0.73 ng/dl, white blood count (WBC) 4.1 K/ul, hematocrit (HCT) 28.9 vol%, hemoglobin (Hb) 9.6 g/dl, platelet (plt) 122K/ul

## Medications:

On Admission: ferrous sulfate 325 mg daily, fosinopril 40mg daily, furosemide 40 mg daily, potassium chloride SA 16 mEq daily, propranolol SA 60 mg daily, human insulin 70/30 26 units q am and 22 units q pm, folic acid 1 mg daily, thiamine 100 mg daily, therapeutic vitamin with minerals 1 daily, paroxetine 20 mg daily, rabeprazole 20 mg q

am, conjugated estrogen vaginal cream once weekly, and lidocaine jelly for urinary catheter insertion.

## Hospital Course:

Six weeks after admission the patient has recurrent UTI's, continued poor oral intake, her mental status has not significantly improved and continues to wax and wane. There has been no improvement in her depressive disorder. She has become progressively weaker since admission.

## Literature:

Whybrow and Bauer describe the range of behavioral and psychological changes in adults with hypothyroidism in their chapter in the reference text, Werner and Ingbar's *The Thyroid a Fundamental and Clinical Text*. They identify the early changes as nonspecific, which are often described as weakness and inattentiveness, inability to concentrate, slowing of thought processes, and inability to calculate and understand complex questions. Memory for recent events is frequently poor. The ability to perform everyday routine tasks is decreased. As hypothyroidism progresses, drowsiness, with lethargy and difficulty in arousal occur. The patient may sleep for long periods during the day and finally may lapse into stupor or even coma. (Whybrow, 2000)

Whybrow and colleagues studied seventeen unselected adults with thyroid disorder who were hospitalized due to physical problems and were thought to represent "typical" patients. Seven of the patients were in the hypothyroid group, all except one complained of poor recent memory and difficulty in concentration. Their difficulties included problems with simple dollars and cents arithmetic. Several of them complained they could not remember where they had placed items in their home and several women could no longer remember recipes for cooking. They found disturbances in the mental function of both hyperthyroid and hypothyroid patients. Impairment of cognitive function was most apparent in the hypothyroid group with impairment of recent memory and profound difficulties with psychological tests demanding attention, abstraction, and memory. Four of the

hypothyroid group were available for reevaluation after treatment. Three of the four patients showed improvement in cognitive function. In one patient who had a two year history of gradually increasing symptoms there was a dramatic improvement after thyroid replacement therapy. Another patient who had been diagnosed as hypothyroid twelve years earlier, but had discontinued thyroid treatment for at least four years was floridly ill on admission and continued to have some confusion after thyroid replacement therapy. Their results provide evidence that long standing hypothyroidism may result in residual impairment of cognitive function, which persists after thyroid replacement. (Whybrow, 1969)

Lishman states that the diagnosis of hypothyroidism is often missed due to its insidious development and nonspecific nature of early complaints. He reminds us of the 8:1 female to male ratio for hypothyroidism. He also comments on the classic physical features of hypothyroidism which are useful clues when present. His description of the typical hypothyroid patient is one of: mental lethargy, generally dulling of the personality and slowing of all cognitive functions. The family may have noticed the patient taking longer to complete routine tasks, being fatigued, and failing to register events and forgetfulness for daily events. He believes the typical mood change is towards apathy rather than depression. In his experience the treatment of hypothyroidism is highly rewarding. The patient gradually regains vitality, physical symptoms diminish and mental processes return to their usual speed and efficiency. He reports that the majority of patients with serious psychiatric developments can be expected to respond, even those with overt dementia, provided that the interval between disease onset and treatment has not been too long.

Canaris and colleagues studied seventy-six newly diagnosed cases with hypothyroidism and one hundred and forty-seven matched controls to determine the relationship between symptoms and biochemical disease. Their cases had TSH levels >20 micro U/ml and a decreased total or free thyroxine level. Even in this group patients with no changed symptoms had a 19% chance

of being hypothyroid. The presence of classic symptoms is suggestive of hypothyroidism, but their absence does not exclude disease. The only three symptoms that differed between cases and controls were: hoarse voice, dry skin and muscle cramps.

Clarnette and Patterson completed a literature search to determine if treatment of hypothyroidism resulted in improvement of mental status in “demented” patients. They found two fairly well documented case reports of demented people who showed cognitive improvement after thyroxine replacement. They mentioned Clarfield’s review of 32 studies of dementia patients including 2781 cases, only 18 (0.65%) of which were documented as being associated with hypothyroidism. One completely reversible case was documented, but the patient was only followed for five months. Six cases had partial recoveries, three did not improve and three deteriorated.

Whether or not to treat so called “subclinical” hypothyroidism is controversial. Cooper has recently published a “Clinical Practice” discussion in the *New England Journal of Medicine* which comments on screening recommendations, treatment recommendations and provides a general discussion. A pair of editorials on subclinical hypothyroidism has recently been published in the *Journal of Clinical Endocrinology and Metabolism*. McDermott and Ridgway favor treatment, while Chu and Crapo believe treatment is seldom needed.

Whether or not thyroxine therapy improves psychiatric, quality-of-life, or hypothyroid symptoms associated with subclinical hypothyroidism is unsettled. Chu and Crapo described five placebo controlled trials which assessed this issue, two showed statistically significant improvement, one suggested benefit with a 24% difference in response between placebo and thyroxine, and the other two studies showed no clear benefit of thyroxine therapy. Their reading of the data suggests that

only those patients with more severe subclinical hypothyroidism (average TSH levels greater than 11mU/L) would benefit from thyroxine therapy.

## Comment:

Our patient was started on thyroxine therapy by geropsychiatry, most likely as an augmentation strategy for depression thought to be refractory to paroxetine. The antidepressant was changed to mirtazapine and the dose was increased to 30 mg daily. There has been no clear improvement in her “depression”. The results of her formal mental status testing are consistent with both hypothyroidism and dementia.

If we assume the patient has subclinical hypothyroidism, not a nonthyroidal sick syndrome, we know that there have been cases of dramatic improvement in cognitive function after thyroxine therapy in some patients. In those patients who improved, the benefit continued as long as they remained euthyroid.

In this case a trial of thyroxine would be reasonable. If there has been no cognitive improvement within a month after she becomes euthyroid, hypothyroidism as the cause of her cognitive decline would not be supported. After an adequate trial the improvement, if any, would need to be weighed against the risks of thyroxine therapy in a patient with known cardiac disease. Then a final decision on the status of continued thyroxine therapy could be made. The American Thyroid Association and several other groups referred to in Cooper’s recent discussion provide monitoring guidelines for patients of chronic thyroxine therapy.

**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](mailto:donna-brus@uiowa.edu).



**Donna Brus, Editor**

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## FDA DRUG/BIOLOGIC APPROVALS

Generic Name (FDA Therapeutic Classification) <i>Trade Name</i>	Sponsor (Approval Date)	Valid <i>IDIS</i> Drug Term Drug Number ( <i>IDIS</i> Citations)*	Indication/Use	Valid <i>IDIS</i> Disease Term Modified ICD-9-CM Number
<b>Fulvestrant</b> (1S**) <i>Faslodex</i>	AstraZeneca (Apr. 25)	FULVESTRANT 10100004 (19 citations)	Treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.	NEOP, MGN-Female Breast 174.
Ibritumomab Tiuxetan (NA***) <i>Zevalin</i>	IDEC Pharm. Corp. (Feb. 19)	IBRITUMOMAB 82000454 (7 citations)	Treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma including patients with Rituximab refractory follicular non-Hodgkin's lymphoma. The therapeutic regimen includes Rituximab, Indium-111 Ibritumomab Tiuxetan, and Yttrium-90 Ibritumomab Tiuxetan.	NEOP, MGN-Lymph/Histio NEC 202.
<b>Interferon beta-1a</b> (NA) <i>Rebif</i>	Serono, Inc. (Mar. 7)	INTERFERON BETA-1A 14000205 (144 citations)	Treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability.	Sclerosis, Multiple 340.
<b>Olmesartan Medoxomil</b> (1S) <i>Benicar</i>	Sankyo Pharma (April 25)	OLMESARTAN 24080412 (3 citations)	Treatment of hypertension.	Hypertension 401.

\* Through May 2002 Update. Complete bibliographic citations will be provided upon request.

\*\* New molecular entity given standard review by FDA.

\*\*\* Not applicable.

### 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 February 2002 through April 2002. *IDIS/CD-ROM* was searched to retrieve key articles relevant to the new drugs and their approved uses.

### **Fulvestrant**

Robertson JF, Nicholson RI, Bundred NJ et al. Comparison of the short-term biological effects of 7alpha-[9-(4,4,5,5,5-pentafluoropentylsulfinyl)-nonyl]estra-1,3,5, (10)-triene-3,17beta-diol (Faslodex) versus tamoxifen in postmenopausal women with primary breast cancer. *Cancer Res* 2001;61:6739-6746. (*IDIS* Article Number 469822). ***Investigators in a partially blinded, randomized, multicenter study compared the effects of a single dose of fulvestrant (50, 125 or 250 mg I.M.) to tamoxifen (20mg. oral) or oral placebo for 14 to 21 days before tumor resection surgery in 200 postmenopausal women with breast cancer.***

### **Ibritumomab Tiuxetan**

Witzig TE, White CA, Wiseman GA et al. Phase I/II trial of IDEC-Y2B8 radioimmunotherapy for treatment of relapsed or refractory CD20+ B-cell non-Hodgkin's lymphoma. *J Clin Oncol* 1999;17:3793-3803. (*IDIS* Article Number 438152). ***Investigators conducted a multicenter phase I/II study to determine the maximum tolerated dose of IDEC-Y2B8 (Y90 Zevalin) and to further evaluate safety and efficacy in 51 patients with histologically confirmed relapsed or refractory low-grade or follicular B-cell non-Hodgkin's lymphoma.***

### **Interferon beta-1a**

Ebers GC, Hommes O, Hughes RA et al. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) study group. *Lancet* 1998;352:1498-1504. (IDIS Article Number 415658). ***In a two year double-blind, placebo controlled multicenter trial, investigators assessed the effects of subcutaneous recombinant interferon beta 1a (22 or 44 micrograms three times weekly) in 560 patients with relapsing/remitting multiple sclerosis with Kurtzke expanded disability status scores of 0-5.0 [ONE OF TWO PIVOTAL STUDIES ON WHICH FDA APPROVAL WAS BASED.]***

Li DK, Paty DW, Ebers GC et al. Magnetic resonance imaging results of the PRISMS trial: a randomized, double-blind, placebo-controlled study of interferon-beta1a in relapsing-remitting multiple sclerosis. *Ann Neurol* 1999;46:197-206. (IDIS Article Number 433793). ***Investigators report the MRI results of the PRISMS study. (see above)***

King J, Mitchell P, Joubert J et al. PRISMS-4: Long-term efficacy of interferon-beta-1a in relapsing MS *Neurology* 2001;56:1628-36. (IDIS Article Number 466251). ***This article reports the results of the two year extension of the PRISMS study. (see above)***

### **Olmesartan Medoxomil**

Neutel JM. Clinical Studies of CS-866 (Olmesartan), the newest angiotensin II receptor antagonist. *Am J Cardiol* 2001;87:37C-43C. (IDIS Article Number 464205). ***This article is a review of efficacy and safety data from seven randomized, double-blind, placebo-controlled, parallel-group phase 2 and phase 3 studies in which CS-866 (once daily monotherapy) was used to treat 2145 patients with essential hypertension.***

Song JC and White CM. Olmesartan medoxomil (CS-866): an angiotensin II receptor blocker for treatment of hypertension. *Formulary* 2001;36:487-499. (IDIS Article Number 466999). ***This article is a comprehensive review of olmesartan medoxomil.***

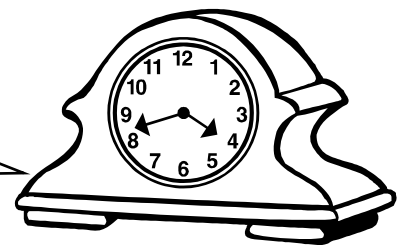
Additional information on these newly approved drugs will be available in the FDA Approval Package (an official United States Food and Drug Administration [FDA] document) that is compiled for new drugs following approval. This document includes reviews of the pivotal and supportive clinical studies conducted during the approval process. These studies are often not published elsewhere. FDA Approval Packages are indexed and included as part of the IDIS database. Use descriptor *155 FDA APPROVAL PACKAGE* in combination with the valid drug term to retrieve these documents from the database



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

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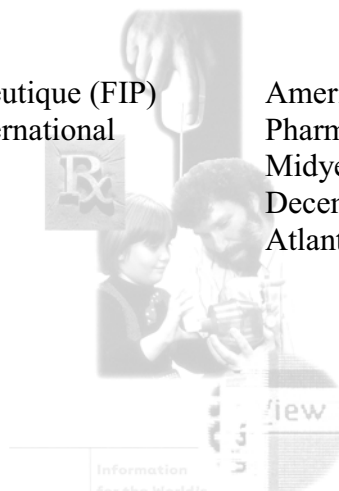
# 2002 EXHIBIT SCHEDULE

American Association of Colleges of Pharmacy  
(AACP) Annual Meeting - Booth #23  
July 12 - 17, 2002  
Kansas City, MO

American College of Clinical Pharmacy  
(ACCP) - Booth #737  
October 20 - 23, 2002  
Albuquerque, NM

Federation Internationale Pharmaceutique (FIP)  
Pharmacy World Congress and International  
Congress of FIP  
August 31 – September 5  
Nice, France

American Society of Health-System  
Pharmacists (ASHP)  
Midyear Clinical Meeting (MCM)  
December 8 - 12  
Atlanta, GA



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