ATTACHMENT A
PAXIL ADVISORY BOARD MEETING

A PROPOSAL FOR ONE PSYCHIATRIST ADVISORY BOARD MEETING

Program Date: November 5-7, 1993

Proposed to:

Bonnie Rossello
SmithKline Beecham

Proposed by:

John A. Romankiewicz, PharmD
Scientific Therapeutics Information, Inc

Revised
October 1, 1993

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WB 085321
PURPOSE

The purpose of this proposal is to outline a description, services, timing, and costs for organizing and running one psychiatrist advisory board meeting with members of the PAXIL Advisory Board. The first meeting will be held from November 5-7, 1993 in Palm Beach Florida.

The purpose of the Advisory Board Meeting is to assemble the members of the PAXIL Advisory Board to provide an exchange of scientific and marketing information regarding PAXIL and related topics. Comments on the information concerning quality, application, and practical suggestions on the best vehicle for distribution, will be solicited. In addition, helpful ideas and advice on issues faced by the PAXIL Marketing Team will be sought.

The information obtained at these meetings will be recorded in a report that will highlight key points and will serve as a reference source for future use.
COST SUMMARY

• Developmental fees, attendance time, estimated travel expenses for STI. $37,400
• Meeting with Chairman, October 11 $2,800
• Slide development, estimated $13,000
• Advisory Board airfares, estimated $40,000
• Meeting Report $12,500
• Background paper preparation: 4 topics $12,000

TOTAL: $117,700
DESCRIPTION

A description of the key components of the Advisory Board Meeting include:

1. The meeting will be held over a three-day period. Day I will be a travel day with a dinner reception held in the evening. Day II and Day III will each have a half-day session held in the morning, concluding with lunch. Departure will be scheduled for the afternoon of Day III.

2. The meeting program will consist of a combination of lectures and discussions. Ample opportunity will be provided for discussion of concepts, new research, and new areas of direction for PAXIL.

3. Selected Advisory Board members may be asked to prepare a presentation relevant to the specific meeting.

4. Each meeting will be a closed meeting. The audience will consist of the Advisory Board members (up to 15), individuals from SmithKline Beecham, and two editors from STI.

5. Each Advisory Board member will receive an honorarium.
AGENDA AND FACULTY

A formal agenda for each meeting will be prepared in advance of each meeting after consultation with SmithKline Beecham. The agenda included below is a sample agenda for the 1993 Advisory Board Meeting. Topics are included without faculty. Briefings on the data available with PAXIL and issues that SmithKline Beecham wants to address are necessary. This agenda will be completed after consultation with the sponsor.

SMITHKLINE BEECHAM PSYCHIATRIST ADVISORY BOARD MEETING

November 5 - 7, 1993

Ritz Carlton Hotel
Palm Beach, Florida

Friday, November 5

Afternoon    Arrival and Hotel Check-in
7:00 PM       Cocktail Reception
8:00 PM       Dinner

Welcoming Remarks by
David Brand, Vice President,
SmithKline Beecham
Saturday, November 6

7:00 AM 
Breakfast

8:00 AM 
Agenda and Objectives
Charles B. Nemeroff, MD, PhD, Chairman

• Strengthen Paxil profile
• Identify competitor deficits/strengths
• Evaluate clinical research/promotional programs
• Generate information for use in promotion/education
• Strategize to reach primary care physicians

8:10 AM 
Overview of Paxil Market Experience and Success
Bonnie Rossello, Paxil Senior Product Manager, SmithKline Beecham

8:30 AM 
Comparison of Paxil with Marketed and Investigational SSRIs
Jerrold F. Rosenbaum, MD (suggested)

• Pharmacology
• Pharmacokinetics
• Indications/efficacy
• Adverse effects

9:00 AM 
Advisory Board Reaction and Comment
Charles B. Nemeroff, MD, PhD, Chairman, Moderating

• Comments
• Controversies
• Summarize strengths/weaknesses of all agents

9:30 AM 
Coffee Break
AGENDA AND FACULTY (continued)

Saturday, November 6 (continued)

10:00 AM  Review of Paxil Clinical Research Program
           David E. Whealon, MD, Vice President,
           SmithKline Beecham
           • Recently completed studies
           • Ongoing studies
           • Future studies

11:00 AM  Advisory Board Reaction and Comment
           Charles B. Nemeroff, MD, PhD, Chairman, Moderating
           • Assessment of research program
           • Suggestions for use of data
           • Recommendations for future studies, indications

11:30 AM  Review of Paxil Promotion
           Brian Lortie, Paxil Product Manager,
           SmithKline Beecham
           • Overview of Paxil promotional program
           • Compare/contrast with competitors' promotional efforts

12:00 PM  Advisory Board Reaction and Comment
           Charles B. Nemeroff, MD, PhD, Chairman, Moderating
           • Assessment of promotional program - by psychiatrists versus primary care physicians
           • Assessment of competitors' promotion
           • Suggestions for additional programs/future directions

12:30 PM  Luncheon
AGENDA AND FACULTY (continued)

Saturday, November 6 (continued)

1:30 PM  Open Forum: Long-Term Outlook for Depression Treatment
          Charles B. Nemeroff, MD, PhD, Chairman
          ● Unmet needs in therapy
          ● Impact of health care reform
          ● Role of psychiatrists, primary care physicians
          ● What is industry involvement?
          ● Future treatment of depression

2:15 PM  Adjourn

2:30 PM  Afternoon at leisure

7:00 PM  Cocktails

8:00 PM  Dinner

Sunday, November 7

7:00 AM  Breakfast

8:00 AM  Breakout into Workshops

Workshop 1  Paxil versus Competitors
            Facilitated by Charles B. Nemeroff, MD, PhD
            Goals: Differentiate Paxil from competitors on
            basis of P450, dose titration, sedation,
            activation, weight loss/gain, sexual dysfunction

Workshop 2  Profile of Paxil Patients
            Facilitated by James C. Ballenger, MD
            Goals: Identify 4 or 5 patient subtypes
            suitable for treatment with Paxil
Sunday, November 7 (continued)

Workshop 3  Reaching the Primary Care Physician
Facilitated by *Psychiatrist with knowledge of primary care and presentation of depression in this setting
Goals: Generate recommendations for educating primary care physicians about depression, appropriate treatment, and use of Paxil

8:00 AM    Workshop 1: Paxil versus Competitors (Group A)
            Workshop 2: Profile of Paxil Patients (Group B)

9:15 AM    Break

9:30 AM    Workshop 3: Reaching the Primary Care Physician (Group A)
            Workshop 1: Paxil versus Competitors (Group B)

10:45 AM   Break

11:00 AM   Workshop 2: Profile of Paxil Patients (Group A)
            Workshop 3: Reaching the Primary Care Physician (Group B)

12:15 PM   Luncheon

1:30 AM    Departure for all

* For these sessions, STI in conjunction with SmithKline Beecham and the Moderator will develop a series of questions on key issues with PAXIL that are aimed at acquiring information.
ADVISORY BOARD MEMBERS*  

ADVISORY BOARD OF PSYCHIATRISTS  
(confirmed as of September 29, 1993)

James C. Ballenger, MD  
Chairman, Dept of Psychiatry  
Director, Institute of Psychiatry  
Medical University of South Carolina  
Charleston, SC 29425

John G. Csernansky, MD  
Gregory B. Couch Associate Professor  
Department of Psychiatry  
Washington University Medical School  
St. Louis, MO 63110

Joseph Deltito, MD  
Director, Anxiety and Mood Disorders Program  
Assoc Professor of Clinical Psychiatry  
New York Hospital  
Cornell Medical Center  
White Plains, NY 10605

David L. Dunner, MD  
Professor and Vice Chairman for Clinical Services  
Dept of Psychiatry and Behavioral Sciences  
University of Washington  
Seattle, WA 98105

Robert Hirschfeld, MD  
Chairman  
Dept of Psychiatry and Behavioral Sciences  
University of Texas Medical Branch  
Galveston, TX 77555

Charles B. Nemeroff, MD, PhD  
Professor and Chairman Dept of Psychiatry and Behavioral Sciences  
Emory University School of Medicine  
Atlanta, GA 30322

Charles F. Reynolds, III, MD  
Director, Sleep Evaluation Center Professor of Psychology and Neurology  
Western Psychiatric Institute and Clinic  
Pittsburgh, PA 15213

Jerrold F. Rosenbaum, MD  
Associate Professor of Psychiatry  
Harvard Medical School  
Chief, Clinical Psychopharmacotherapy Unit  
Massachusetts General Hospital  
Boston, MA 02114

Steven Schleifer, MD  
Professor and Chairman Dept of Psychiatry  
UMDNJ  
Newark, NJ 07103

David V. Sheehan, MD  
Professor of Psychiatry  
Director, Clinical Research  
University of South Florida Psychiatry Center  
Tampa, FL 33613

* Additional Advisory Board Members are being recruited.
SERVICES

The services and costs for this Advisory Board meeting assume that SmithKline Beecham will provide all logistical arrangements. STI will provide program design and content, editorial development, and faculty liaison services.

STI Editorial Services

STI will work in conjunction with SmithKline Beecham to provide the following:

- Identify and develop program content/agenda.
- Identify and recruit Advisory Board Members
- Research and prepare background material for mailing to Advisory Board prior to meeting.
- Provide slide services as needed for presenters.
MEETING EDITORIAL COSTS

Our costs are based on program development work, editorial activity, writing, proofreading, correspondence (usually express mail) with Advisory Board members, SmithKline Beecham and others as needed to insure a high quality, credible, and useful program for SmithKline Beecham and Advisory Board members. Costs are as follows:

**Editorial Development:** Liaison with board members including recruitment and travel arrangements of board members and SmithKline Beecham, content outline development, preparation of moderator for meeting, authoring one presentation (Rosenbaum) and discussion questions (fee).

COST: $30,000

**STI Airfare Expenses:** Two STI editors (coach).

COST: $2,000†

**Per Diem Expenses:** Two STI editors: 3 days each.

COST: $1,500

**STI Meeting Attendance and Travel Time:** Two editors onsite, plus travel time (fee). Assumes three days.

COST: $3,900

**Consulting Fee:** Up to 20 Advisory Board members as follows: Chairman - $5,000; 3 presenters/moderators @ $4,000 each; 16 (estimated) @ $2,500 each.

(SB TO PAY)

**Slide Development** STI will work with the faculty to develop high quality and professional presentation slides. Our costs for slides are $130.00 per slide if we have 2 weeks or more to work with and $170.00 if we have less than two weeks to work. We estimate 100 slides for this program.

COST: $13,000*

† Pass through cost
* STI will bill for the actual number of slides developed.
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**Meeting with Chairman:**
One visit with Chairman in Atlanta on October 11, 1993. Two editors @ $650 each (fee) plus travel expenses estimated at $1,500 (air and ground transport)

**COST:** $2,800

**Board Travel Expenses:**
First Class air travel for 20 Advisory Board Members.

**COST:** $40,000†

**TOTAL (Editorial development costs):** $93,200

† Pass through cost.
MEETING REPORT

STI will transcribe the audiotapes (meeting plus one of each workshop) and provide a synopsis of the key points from the meeting. The report will be issued within one month of the meeting. We estimate the report to be up to 50 doublespaced typewritten pages. An executive summary will be included.

COSTS: $12,500
BACKGROUND PAPERS

Purpose: We propose to develop succinct background papers that will provide a literature based review of the facts regarding issues associated with Paxil. These papers will outline the information needed to come to a consensus on the specific issues that will be discussed in the workshops.

Description:
Each background paper will be up to 10 typewritten, double spaced pages in length and will include pertinent references. A statement of the issue will initiate the paper with a detailed analysis of data supporting or refuting the issue to follow. Background papers will be developed on the following topics:

1. P450 and drug interactions with SSRIs
2. Identification of patient types for Paxil therapy
3. Dose titration needs with SSRIs
4. Sedation and SSRIs

Costs: The costs associated with development of these background papers include literature research, technical writing and editing, client review and comments, preparation of two drafts, timing (one month), word processing, copy editing and proofreading, distribution to advisory board members in advance of meeting, and management needed to develop these background papers on a timely schedule.

COST (per paper): $3,500
COST (4 papers): $12,000*

* A discount is provided for development of all four developed simultaneously because we can take advantage of economies of scale.
PAYMENT SCHEDULE

To be invoiced immediately $58,850

To be invoiced upon completion of the meeting
November 4-5, 1993 $58,850

$117,700

WB 085336
ATTACHMENT B
From: Sally Laden <sally.laden@cox.net>
To: eric.m.dube@gsk.com
Subject: Proposal for 2 review articles
Date: 07/28/2003 09:40:30 (GMT-05:00)

Dear Eric:

Thank you for thinking of me for the Safety in Breast Feeding and the Tolerability of PaxilCR review articles. A proposal for both is attached. Please review and contact me with questions. As we discussed on Friday, I am not able to start work on these papers until September, but if we decide to move forward, I will reserve that month for these projects.

Two other questions:

1) Lydia Lewis from the DBSA asked me to be the writer for their upcoming dual diagnosis consensus meeting this November. She mentioned that Scott committed GSK to funding the writing costs for the consensus statement. Lydia is asking if GSK will be able to paying me directly rather than offering the DBSA a grant for the cost of the writing. I am having problems connecting with Scott. If you see him in the near future, would you inquire about this? I would submit the proposal directly to GSK and bill GSK directly. (Thanks)

2) Is there a problem with my invoice for writing Dwight Evans, editorial for the DBSA, comorbidity issue to Biological Psychiatry? I submitted it over a month ago and was wondering about the status. If the payment cycle >30 days, so be it. I was just wondering.

Thanks again Eric. I look forward to working with you again.

Sally Laden  MSE Communications

898 Cahill Court Cheshire, CT06410
T 203 y271-1047  F 203 y271-1054  E sally.laden@cox.net

- New business proposals.doc

Attachments: New business proposals.doc;embedded picture.bmp
ATTACHMENT C
Mood Disorders and Medical Illness: A Major Public Health Problem

Despite efficacious and widely available antidepressants and psychotherapeutic interventions, the psychosocial and medical burden of depression is increasing. In fact, the World Health Organization projects that depression will continue to be prevalent, and by the year 2020, will remain a leading cause of disability, second only to cardiovascular disease (Michaud et al 2001). Although we do not know with certainty why rates and disability associated with depression are increasing, it is likely that this mood disorder continues to be remarkably under-recognized and under-treated. Depression frequently occurs in the context of chronic medical illness, and it is only relatively recently that the research community has turned its attention to the relationship between depression and chronic medical conditions. However, there is much work yet to be done. The recently released Institute of Medicine report (2003) acknowledged depression as one of a number of chronic conditions that requires priority action, but did not address the importance of comorbid depression and medical illness.

The relationship between depression and medical illnesses is complex. A chronically ill patient who also is clinically depressed may experience enhanced morbidity, a poorer prognosis, and even increased mortality from the medical diagnosis. Simply put, depression makes everything worse. But the association with depression goes beyond the effects of comorbidity on the course and outcome of a medical illness. A burgeoning body of evidence has now demonstrated that the relationship between depression and certain medical illnesses may indeed be bidirectional in nature. Depression may be both a cause and a consequence of some medical illnesses, such as cardiovascular disease, stroke, HIV/AIDS, cancer, and epilepsy.

In recognition of the need to increase awareness about this topic and improve the quality of life for persons with depression, the Depression and Bipolar Support Alliance, the world’s largest patient advocacy organization, convened a two-day, multidisciplinary consensus conference on November 12, 2002 in Washington, DC. Nearly 50 experts in the fields of psychiatry, cardiology, immunology, oncology, neurology, endocrinology, internal medicine, family medicine, federal health care agency policy and research, and patient advocacy participated in this process. Formal presentations centered around the perspectives and goals of the National Institutes of Health and the Food and Drug Administration, the personal and societal burden of depression and medical illness, and the epidemiology, mechanisms, diagnosis, treatment, and prognosis of depression in the context of cardiovascular disease, cancer, HIV/AIDS, stroke, neurologic diseases, diabetes, osteoporosis, obesity, and chronic pain. Workgroups met to discuss specific issues related to these topics and on the second day, workgroup leaders presented their findings and facilitated open discussions from the group.

Burden of Mood Disorders and Medical Illness

The functional impairment associated with depression contributes significantly to the economic burden of chronic medical illness. Depression also is becoming recognized as a cause of increased morbidity and mortality in chronic medical illness. As reviewed by Katon (2003), medical costs for patients with major depression are approximately 50% higher than the costs of chronic medical illness alone. In addition, Katon (2003) underscores the equally important, but often less appreciated, effects of depression on adverse health behaviors, such as smoking, unhealthy diet, sedentary lifestyle, and poor adherence to medical regimens (e.g., cardiac rehabilitation). The findings from a number of studies have established that major depression is associated with significant functional impairment, lost work productivity, occupational disability, and increased health care resource utilization, and that effective treatment restores functioning. Simon (2003) reviews these data in the context of evidence from recent cross-sectional, longitudinal, and treatment studies of depressed patients with and without arthritis, chronic obstructive pulmonary disease, diabetes, or heart disease. This emerging body of evidence demonstrates that depression significantly increases the burden of functional impairment in medical illness, and that treatment reduces disability and health service costs. The effect of other mood disorders, such as dysthymia or bipolar disorder, on the burden of chronic medical illness is remarkably understudied.

Cardiovascular Disease

It is now recognized that major depression and bipolar disorder are associated with increased rates of death from
coronary heart disease (CHD), and that major depression or depressive symptoms increase the risk of incident CHD (Musselman et al 1998). As reviewed by Rudisch and Nemeroff (2003), as many as 27% of patients with CHD have major depression, but a substantially larger number of cardiac patients have subsyndromal depressive symptoms. Depression is a particularly lethal development for patients with acute myocardial infarction (MI). In the United States, there are approximately 150,000 deaths in the first year after an initial MI, and Carney and Freedland (2003) estimate that at least 90,000 of these deaths may be related to post-MI depression. The cumulative body of evidence in support of an association between depression and cardiovascular disease is large and impressive; Carney and Freedland (2003) evaluate this literature and outline future directions for research, including studies that will better elucidate the role of depression in the development and progression of atherosclerosis, ischemia, and arrhythmias.

One particularly diverse and robust field of research is dedicated to better understanding the mechanisms that underlie the relationship between depression and cardiovascular disease. In their paper, Joynt and colleagues (2003) overview seven probable mechanisms associated with depression that may be related to cardiovascular disease: noncompliance with cardiac rehabilitation and medical regimens; risk factor clustering (e.g., smoking, hypertension, diabetes, hypercholesterolemia, obesity); hypothalamic-pituitary-adrenal (HPA) axis hyperactivity and cortisol elevation; decreased heart rate variability; elevated plasma levels of pro-inflammatory cytokines leading to atherosclerosis; platelet activation and hypercoagulability; and psychological stress.

The demonstrated adverse effect of depression on the risk of new and progression of established CHD has spurred the next emergent area of clinical study in this field: the consequences of depression treatment on cardiovascular morbidity and survival. As noted in the paper by Roose (2003), findings from the few open-label or randomized, controlled clinical trials suggest that the selective serotonin reuptake inhibitors (SSRIs), bupropion, and certain psychotherapeutic interventions are safe and effective treatment of depression in patients with CHD. The tricyclic antidepressants (TCAs) increase heart rate, cause orthostatic hypotension and conduction delays, have been shown to increase the risk of cardiac mortality, and should be avoided in this patient population. There is one published placebo-controlled trial, which suggests that SSRI treatment of depressed post-MI patients may improve outcome and increase survival, but this study was not adequately powered to find significant changes in these cardiac disease outcomes. Thus, it is still not known whether treatment of depression enhances the outcome of the cardiac disease. Further study is clearly needed.

Cancer

As with cardiovascular disease, there is a large and growing body of evidence in support of a relationship between depression and cancer. Research efforts have focused on depression as a risk factor for cancer, depression as a consequence of cancer, and the dynamics of comorbid depression and cancer. Large population studies suggest that depressed mood or stressful life events may increase the risk of cancer. Although it is acknowledged that these observations of increased risk may be due in part to earlier, undetected malignancies or factors other than depression (Lillberg et al 2003; Penninx et al 1998), these findings are compelling and further study is warranted.

Depression also is a common occurrence in patients with a wide range of different malignancies and often prevents patients from complying with treatment regimens and other health-promoting behaviors, thus worsening the prognosis. A diagnosis of cancer represents a significant life stressor, which in vulnerable persons can precipitate an episode of depression. In addition, patients with cancer may develop "sickness behavior" or depressive syndromes due to proinflammatory cytokine activation that is the result of tumor cell burden, tissue destruction, radiation treatments, and chemotherapy. The papers by Raison and Miller (2003) and Spiegel and Giese-Davis (2003) review the relationships between depression and cancer and offer insight into disease progression and treatment. Of immediate clinical utility are the findings of studies showing that pretreatment with serotonergic antidepressants can prevent neurotoxicity and clinical depression in patients treated with interferon-alpha.

HIV/AIDS

Mood disorders, including depression and mania, are prevalent in persons with human immunodeficiency virus (HIV) disease and may be associated with impaired quality of life, neurocognitive and functional impairment, and poor adherence to antiretroviral therapy. In addition, emerging data suggest that depression is associated with declining CD4 cell counts, accelerated disease progression, and increased mortality. In their paper, Cruess and colleagues (2003) discuss the negative impact of mood disorders on HIV/AIDS and review evidence for safety and efficacy of antidepressants, mood stabilizers, and novel pharmacotherapies in this population (Evans et al 2002a). Leserman (2003) also reviews this topic, but with a focus on the biological mechanisms underlying the relationship between mood disorders and HIV disease.
and the immune effects that result from this comorbidity (Leserman et al 1997; Evans et al 2002b). Patients with HIV/AIDS and comorbid depression are a significantly underserved and understudied population. Further epidemiologic, biological, and therapeutic studies are urgently needed to better understand the nature of this comorbidity, increase case-finding, and develop effective treatment strategies.

Neurologic Disease

This special issue also includes papers devoted to the topics of depression and comorbid neurologic disorders, such as stroke, Parkinson’s disease, Alzheimer’s disease, and epilepsy. Of these neurologic disorders, the relationship between mood disorders and cerebrovascular accidents is particularly well-studied. As reviewed by Robinson (2003), depression is common in poststroke patients, with reported prevalence rates of approximately 20%; bipolar disorder is less common. There is no standardized diagnostic approach for poststroke depression, and the controversies surrounding various approaches are summarized by Robinson (2003). The findings of treatment studies showing efficacy of antidepressants, electroconvulsive therapy, psychostimulants, and cognitive behavioral therapy in patients with poststroke depression are of considerable clinical importance. Importantly, treatment of depression improves measures of function and cognition and may result in improved survival. Evidence that antidepressants may prevent poststroke depression offers hope. As with many other medical comorbidities, depression may increase the risk of stroke, and the findings of two large epidemiologic studies support the role of depression as a risk factor for stroke. These findings further underscore the importance of identifying the underlying biological mechanisms associated with depression comorbidity.

Depression occurs in roughly half of patients with Parkinson’s disease and is associated with significant impairment, including reduction in fine motor skills and cognitive function. In their paper, McDonald and colleagues (2003) review the distinct presentation of depression in Parkinson’s disease. Clearly, epilepsy is a risk factor for depression; however, recent evidence suggests that depression may increase the risk for epilepsy by 4- to 6-fold. Further studies are needed to better characterize this complex relationship.

Call for Action

The contributions made by this conference and the papers published in this special issue of Biological Psychiatry should not simply be measured by the quality and quantity of the data, which are impressive. Rather, the strength of this publication also lies in the fact that the views of experts from widely divergent fields of clinical and scien-
sific endeavor resonate along 4 basic themes: 1) Depression is very common in chronic medical illness; 2) Comorbidity with depression inevitably hinders recovery and worsens prognosis; 3) Medical illness is a risk factor for depression because of psychosocial stressors, functional impairment, and other biological mechanisms (e.g., Parkinson’s disease); and 4) Depression may figure prominently as an etiologic factor in the onset and course of medical illness, particularly cardiovascular disease, stroke, HIV/AIDS, cancer, and epilepsy. The latter observation is truly remarkable. Much more research is needed to better understand this bidirectional relationship and identify possible common pathogenic, mechanistic pathways that link depression and serious medical illness.

These are powerful messages that must not be ignored. The weight of evidence is so persuasive that there should never again be a valid reason for not aggressively seeking out and treating depression in medically ill patients. Increasing awareness, reducing stigma, and maintaining a high level of vigilance for depression in medically ill patients must become a priority for clinicians. In addition, the efforts of the research communities must continue to better elucidate the prevalence, risk profile, diagnostic criteria, treatment, and biological underpinnings of the comorbid relationship between depression and medical illness. Only by furthering research efforts and aggressively diagnosing and treating depression, will we be able to achieve substantive gains in health care and in our patients’ quality of life.

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We acknowledge Sally K. Laden for editorial support.

References


RECOGNITION AND TREATMENT OF PSYCHIATRIC DISORDERS:
A PSYCHOPHARMACOLOGY HANDBOOK FOR PRIMARY CARE PHYSICIANS

First Edition

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Developed under an educational grant from:
SmithKline Beecham Pharmaceuticals
Philadelphia, Pennsylvania

PRELIMINARY DRAFT/February 25, 1997
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Before prescribing any medication, review the complete prescribing information, including indications, contraindications, warnings, precautions, and adverse effects.

This publication is prepared under an educational grant from SmithKline Beecham Pharmaceuticals by Scientific Therapeutics Information, Inc, 505 Morris Avenue, Springfield, New Jersey 07081, USA; telephone (201) 376-5655; FAX (201) 376-0611.

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Psychopharmacology Handbook.1112(51097)/Page 2

WB 193560
PREFACE

Under development
INTRODUCTION

Under development; will include overview on how to use the handbook, format/contents. Will state that the book focuses on psychopharmacology rather than psychotherapy and only adults are considered. Focus is on psychiatric disorders most commonly seen in primary care.
OVERVIEW OF PSYCHIATRIC DISORDERS

ALZHEIMER’S DISEASE

Alzheimer’s Disease (AD) is the most common primary, progressive degenerative dementia in the elderly and the fourth leading cause of death in the United States (Keefover, 1996; Raskind, 1993). At an annual cost of more than $67 billion in the US alone, AD has important public health implications, especially in concert with the unparalleled growth of the aged population (Keefover, 1996).

Epidemiology

Alzheimer’s disease afflicts up to 4 million US adults (Keefover, 1996), a figure that may double by the year 2000 (Price et al, 1995). The prevalence of AD clearly increases with advancing age and some estimate that up to 50% of US adults older than 85 years of age have the disorder (Evans et al, 1989). Overall estimates of the incidence of AD (1%/y) are hindered by a lack of reliable data (Keefover, 1996). The presence of AD greatly reduces life expectancy; median survival is 5 to 8 years after diagnosis (Keefover, 1996) but the illness can persist up to 20 years until death (Cohen, 1995). Life expectancy is lower in men with AD than in women with AD and in also those with significantly impaired cognition at the time of diagnosis. Risk factors for AD are shown in Table 1 (Keefover, 1996).
Table 1. Possible risk factors for AD (Keefover, 1996; Sandson et al., 1995)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Comments</th>
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<tr>
<td>Aluminum ingestion</td>
<td>Unresolved; † aluminosilicate concentrations found in NFT and plaques of persons with AD but aluminum inhalation or ingestion (including aluminum-containing antacids) does not produce AD</td>
</tr>
<tr>
<td>Apolipoprotein E4</td>
<td>Presence of the E4 allele is a strong risk factor for late-onset AD but not a diagnostic test</td>
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<tr>
<td>Diet</td>
<td>Possible trend toward delayed onset of dementia in vegetarians versus heavy meat eaters</td>
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<tr>
<td>Education level</td>
<td>AD occurs more often in undereducated persons</td>
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<tr>
<td>Estrogen deficiency</td>
<td>Postmenopausal women not using estrogen supplements may be at risk for AD</td>
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<tr>
<td>Family history</td>
<td>Positive family history † risk of AD</td>
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<tr>
<td>Female gender</td>
<td>Unresolved whether females are at greater risk for AD than males</td>
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<tr>
<td>Head injury</td>
<td>Head injury causing loss of consciousness or retrograde amnesia has been associated with † risk of AD in men in later life</td>
</tr>
<tr>
<td>Maternal age</td>
<td>Late maternal age may † risk of AD in offspring</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>Unconfirmed association between thyroid disease and AD</td>
</tr>
</tbody>
</table>

See Glossary for abbreviations.

Pathophysiology

Although the cause of AD is unknown, a genetic component is likely (Small, 1996). The primary degenerative central nervous system (CNS)
changes in AD include prominent cerebral atrophy in cortical association areas, neuronal losses, neurofibrillary tangles [NFT], and neuritic or senile plaques. The latter two are hallmark neurohistologic lesions of AD and were first described in the early 1900s by Alois Alzheimer.

Because of these degenerative changes, patients with AD have deficits of several neurotransmitters, primarily acetylcholine (ACH), but also of monoamines (eg, dopamine, norepinephrine, serotonin), somatostatin, and gamma aminobutyric acid (GABA). Low ACH levels may be caused by reduced activity of enzymes (eg, choline acetyltransferase [ChAT], acetylcholinesterase) involved in ACH synthesis (Schneider and Tariot, 1994).

Presentation

Insidious memory loss is the hallmark feature of AD (Table 2); short-term memory loss occurs in the early stages of AD and is eventually followed by long-term memory loss (Price et al, 1995; Raskind, 1995).
Table 2. Typical presentation of AD

- Appears usually after 65 years of age
- Reduced cognitive abilities
  - memory, performance speed, problem-solving skills
- Language disorders (word-finding difficulties, aphasia)
- Altered spatial perceptions, judgment (eg, personal safety)
- Progressive inability to perform or inattentiveness toward activities of daily living and personal hygiene
- Disruptive behavioral changes
  - nonpsychotic (eg, physical and verbal abuse, aggression, agitation, screaming, wandering, uncooperativeness)
  - psychotic (eg hallucinations, simple paranoid delusions)

At least 40% of patients with AD develop disruptive, agitated behavior during the course of the disorder; this behavior may adversely affect cognitive function by interfering with motivation or attentiveness (Raskind, 1993).

Hallucinations and delusions often appear in a patient with AD usually during the early or middle stages of the disorder. In contrast to the more complex, grandiose delusions of schizophrenia, delusions of AD are usually simple, paranoid beliefs related to memory loss. Typical delusions of AD might include perceived theft of money or personal items, a belief that a long-deceased acquaintance is still alive, or a
belief that one's spouse is an imposter. These differences between delusions of schizophrenia and those of AD may explain why antipsychotic drugs are less effective in the latter disorder.

Depression often coexists with AD and can aggravate simple memory loss. In advanced stages of AD, patients have profound dementia, aphasia, and usually are bedridden, incontinent, and unable to remain alone or in a home setting without constant care.

Diagnosis

Dementia is only one possible diagnosis in an older individual with reduced cognitive function. Other causes of impaired memory include that due to normal aging processes, encephalopathies (eg, from anoxia, head trauma), vascular or multi-infarct dementia, or an acute confusional state related to a metabolic, toxic, or infectious disorder (Sandson et al, 1995). These alternative diagnoses should be ruled out.

The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) task force has established commonly used diagnostic criteria for possible, probable, or definite AD (McKhann et al, 1984). However, a definitive diagnosis of AD can only be made on autopsy.
To establish progressive deterioration in memory and cognitive skills, the primary care physician must perform a careful patient evaluation, including a detailed family history, medication history, past medical history, and a complete physical, neuropsychologic, and laboratory workup (Table 3). Referral for neuroimaging studies may be useful in selected cases (McKhann et al, 1984; Price et al, 1995; Sandson et al, 1995).
Table 3. Diagnostic approach to the patient with suspected AD (McKhann et al, 1984; Sandson et al, 1995)

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Goal</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical history</td>
<td>Establish history of progressive memory deterioration and inability to perform tasks.</td>
<td>Interview patient, family, close acquaintances. Obtain detailed family history, medication history (prescription and nonprescription), past medical history (eg, stroke, seizures, head trauma, psychiatric history)</td>
</tr>
<tr>
<td>Clinical examination</td>
<td>Document diagnostic inclusion and exclusion criteria</td>
<td>Perform physical examination, mental status testing (eg, MMSE), neurologic testing</td>
</tr>
<tr>
<td>Neuropsychological evaluation</td>
<td>Provide additional information on diagnosis of dementia</td>
<td>Recognition Span Test, Boston Naming Test, Wechsler Adult Intelligence Scale, Continuous Performance Test, Gollin Incomplete Pictures Test, Wisconsin Card Sorting Test, Philadelphia Geriatrics Center forms'</td>
</tr>
</tbody>
</table>
Table 3 (cont'd). Diagnostic approach to the patient with suspected AD (McKhann et al, 1984; Sandson et al, 1995)

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Goal</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory testing</td>
<td>Enhance diagnostic accuracy</td>
<td>Obtain routine blood, electrolyte, renal, liver, metabolic studies. Also, Vitamin B₁₂, folic acid, thyroid function tests, erythrocyte sedimentation rate, syphilis or HIV (if risk factors present)</td>
</tr>
<tr>
<td>Neuroimaging studies</td>
<td>Identify potentially treatable causes of dementia (e.g., tumors, abscess, subdural hematoma)</td>
<td>CT or MRI</td>
</tr>
<tr>
<td></td>
<td>Identify ↓ regional glucose metabolism and blood flow in parietal and temporal lobes</td>
<td>PET or SPECT (mainly research tools)</td>
</tr>
</tbody>
</table>

See Glossary for abbreviations.
* See McKhann et al, 1984 for more detailed information.
Screening Tools: In the office setting, the Mini Mental State Examination (MMSE) (Folstein et al, 1975), the Blessed Dementia Scale, (Blessed et al, 1968), or the Short Portable Mental Status Questionnaire (Pfeiffer, 1975) may be used to screen a patient in whom dementia is suspected. On the MMSE, a score of 26 or less is abnormal in a high school graduate and a score of 27 to 30 with evidence of cognitive decline should prompt more detailed neuropsychological testing (Peskind, 1996). More detailed neuropsychologic testing as outlined by the NINCDS-ADRDA (McKhann et al, 1984) should follow if clinical suspicion is raised. Patients with AD will show a reduction of 3 to 4 points/y on the Blessed Memory Concentration Test or a reduction of 2 to 3 points/y on the MMSE (Price et al, 1995).

Referrals

A multidisciplinary approach that addresses medical, social, psychological, and environmental issues is needed not only for the patient’s benefit, but also for the family or caregiver’s sake (Cohen, 1995; Sky and Grossberg, 1994). Alzheimer’s disease extracts a substantial burden on the patient’s family and caregivers; these individuals often become the “second patients.” It has been estimated that up to 80% of spousal caregivers experience clinically significant symptoms of anxiety or depression as well as more frequent medical illness associated with chronic stress during the course of the patient’s disorder (Cohen, 1995). Thus, the primary care physician
plays an important role in referring family members or caregivers to local support services (see Glossary) that may alleviate some of these stresses. For example, having the patient attend an "adult day care" setting once or twice weekly may provide the caregiver with sorely needed personal time.

ANXIETY DISORDERS

Panic Disorder
Agoraphobia
Obsessive-Compulsive Disorder (OCD)
Posttraumatic Stress Disorder (PTSD)
Generalized Anxiety Disorder (GAD)
Social Phobia

EATING DISORDERS

Anorexia Nervosa (with subtypes)
Bulimia Nervosa (with subtypes)
MOOD DISORDERS

Depressive Disorders

Mania

Bipolar Disorder

SCHIZOPHRENIA

SLEEP DISORDERS

Primary Insomnia

SOMATIZATION DISORDER

SUBSTANCE USE/ABUSE DISORDERS

Cocaine Abuse

Alcohol Abuse

Opiate/Opioid Abuse
Before prescribing any drug to a patient, readers are encouraged to consult a current and more complete source of prescribing information, such as the *Physician's Desk Reference* (1997), *AHFS Drug Information* (1997), or other similar source. Unless otherwise cited, information in this chapter has been compiled from these and similar secondary resources.

**ANTIDEPRESSANTS**

**BENZODIAZEPINES**

**NONBENZODIAZEPINE ANXIOLYTICS**

**ANTIPSYCHOTICS**

Traditional

Atypical (olanzapine, risperidone, clozapine)

**DRUGS FOR EXTRAPYRAMIDAL SYMPTOMS**
DRUGS FOR BIPOLAR DISORDER

COGNITIVE ENHANCERS

Ergoloid Mesylates

Ergoloid mesylates (Hydergine®, Sandoz Pharmaceuticals Corporation; dihydroergotoxine, dihydrogenated ergot alkaloids) are indicated for symptomatic relief of age-related mental capacity decline (in persons >60 years of age), such as that which might occur in AD (Table 4).

Table 4. Overview of ergoloid mesylate therapy

<table>
<thead>
<tr>
<th>Feature</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Unknown, may ↑ cerebral blood flow</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Rapid oral absorption, extensive hepatic metabolism, drug interactions not reported</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Modest ↑ in cognition</td>
</tr>
<tr>
<td>Safety</td>
<td>Transient nausea, GI disturbances</td>
</tr>
<tr>
<td>Dosing</td>
<td>Start with 1 mg TID; titrate up to 12 mg/d in divided doses; response usually requires ≥ 6 mg/d for 6 months</td>
</tr>
</tbody>
</table>
Mechanism: Ergoloid mesylates may increase cerebral blood flow although the exact mechanism is unknown. Unlike natural ergot alkaloids, this product does not have vasoconstrictive properties.

Pharmacokinetics: Ergoloid mesylates are rapidly absorbed in the gastrointestinal (GI) tract after oral administration and are quickly and extensively metabolized in the liver. Drug interactions have not been reported.

Efficacy: In 12-week studies using the Sandoz Clinical Assessment Geriatric Rating Scale, modest but statistically significant improvements have been observed in mental alertness, confusion, orientation, emotional lability, recent memory, self-care, depression, anxiety, cooperation, sociability, appetite, dizziness, fatigue, and overall improvement in clinical status.

Safety: Ergoloid mesylates are generally well tolerated but can cause transient nausea or other GI disturbances.

Warnings/Precautions: Reversible and potentially treatable causes of dementia should be ruled out before ergoloid mesylate therapy is prescribed. Periodically reevaluate any perceived benefit of therapy to the patient.
Dosing Guidelines: The usual starting dose is 1 mg TID; doses may be increased up to 12 mg/d (divided). Results may not be detected for 3 or 4 weeks and treatment with a minimal dose of 6 mg/d may be needed for at least 6 months to detect any benefit. This product is available in tablet, liquid, and liquid capsule formulations.

Cholinesterase Inhibitors

Because of the known deficit of cortical ACH in persons with AD (ie, the cholinergic hypothesis), drug development research has focused on agents that will restore levels of this neurotransmitter either directly (ie, cholinergic agonists) or indirectly (ie, cholinesterase inhibitors). In 1993, the first cholinesterase inhibitor, tacrine (Cognex®, Parke-Davis; tetrahydroaminoacridine, THA), was approved for the treatment of mild to moderate cognitive impairment of AD. Although tacrine is only modestly effective and carries a relatively significant adverse effect profile, it may offer respite (albeit temporary) for selected patients with AD (Table 5).
### Table 5. Overview of tacrine therapy

<table>
<thead>
<tr>
<th>Feature</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>↑ ACH concentrations via nonspecific inhibition of brain cholinesterase</td>
</tr>
<tr>
<td><strong>Pharmacokinetics</strong></td>
<td>Rapid oral absorption, extensive hepatic metabolism</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>Minimal but significant improvement in ADAS cog, and global impressions in trials lasting ≤30 weeks. High rate of withdrawal due to side effects</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>GI distress, myalgia, ataxia, anorexia (dose-related). ↑ LFTs require extensive and prolonged monitoring</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Start with 10 mg QID (empty stomach, between meals) for ≥ 6 weeks; ↑ to 20 mg QID if LFTs normal and tolerance good. Discontinue if no response in 6 months.</td>
</tr>
</tbody>
</table>

**Mechanism:** Tacrine is a centrally active, reversible, nonspecific cholinesterase inhibitor that increases ACH concentrations by minimizing or preventing its breakdown after ACH is released from functioning cholinergic neurons. Tacrine does not change the natural, progressive course of AD and it is relatively ineffective in advanced stages of AD when few cholinergic neurons remain viable.
Pharmacokinetics: Taken orally, tacrine is rapidly absorbed and has a duration of action of 4 to 6 hours. Food does not affect tacrine absorption if the drug is taken at least 1 hour before meals (i.e., on an empty stomach, between meals if possible). Tacrine is extensively metabolized by hepatic cytochrome P450 enzymes, primarily CYPIA2 (see Table 6) but not CYPIID6. Advanced age and renal disease have no clinically important influence on tacrine elimination. However, liver disease may reduce the elimination of tacrine and its metabolites. Tacrine serum concentrations are 50% higher in females than in males and about 33% lower in smokers than in nonsmokers.
### Table 6. Drug and food interactions with tacrine

<table>
<thead>
<tr>
<th>Substance</th>
<th>Effect of tacrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergics</td>
<td>May interfere with activity of anticholinergics</td>
</tr>
<tr>
<td>Cholinergic agonists (eg, bethanechol), cholinesterase inhibitors (eg, physostigmine), succinylcholine</td>
<td>May have a synergistic effect with these drugs</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Prolongs elimination of theophylline and ↑ plasma concentrations. Monitor theophylline concentrations and ↓ dose accordingly</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Cimetidine ↑ concentrations of tacrine by inhibiting its metabolism</td>
</tr>
<tr>
<td>Food</td>
<td>Food ↓ plasma tacrine levels by one-third; take tacrine between meals if possible</td>
</tr>
</tbody>
</table>

**Efficacy:** Tacrine has been shown to be effective in placebo-controlled trials in patients with mild to moderate probable AD. In two key studies of up to 30 weeks' duration, most patients taking tacrine (20 to 160 mg/d) showed minimal but statistically significant improvement in the Alzheimer’s Disease Assessment Scale (ADAS cog; Rosen et al, 1984)

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and clinician’s global impression measures (Davis et al, 1992; Farlow et al, 1992; Knapp et al, 1994). The ADAS cog examines memory attention, reason, language, and praxis. However, there were a wide range of responses and a substantial number of patients were unable to tolerate tacrine therapy and withdrew from the trials. Importantly, the beneficial effects of tacrine tended to diminish with time, even in patients who experienced an initial beneficial response.

Safety: Tacrine has an extensive adverse effect profile. Common adverse events are nausea, vomiting, diarrhea, dyspepsia, and other GI symptoms, elevated LFTs (see Warnings/Precautions), myalgia, anorexia, and ataxia. Except for LFT abnormalities and myalgia, these effects are dose related. The safety and efficacy of tacrine have not been tested in demented children; tacrine should not be given to pregnant or lactating women (Pregnancy Category C; see Glossary).

Warnings/Precautions: Use tacrine carefully in patients with current or past liver dysfunction (ie, elevated LFTs). Tacrine commonly increases LFTs in persons without a prior history of liver disease and may cause clinically significant sequelae (eg, jaundice). However, prompt withdrawal of tacrine in such circumstances will only rarely result in liver injury and LFTs should return to normal limits within 4 to 6 weeks. Patients who develop clinical jaundice (total bilirubin >3 mg/dL) or those with clinical signs or symptoms of hypersensitivity...
with elevated LFTs should permanently stop tacrine therapy (see Dosing Guidelines below and prescribing information for LFT monitoring advice). Tacrine stimulates cholinergic activity and should be used cautiously in selected patients (Table 7).

Table 7. Cautions related to cholinergic activity of tacrine

<table>
<thead>
<tr>
<th>Tacrine may cause:</th>
<th>Use with caution in:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>&quot;Sick sinus syndrome,&quot; conduction abnormalities, bradyarrhythmia</td>
</tr>
<tr>
<td>↑ Gastric acid secretion</td>
<td>Patients at risk for ulcers (eg, history of ulcer disease, current NSAID users).</td>
</tr>
<tr>
<td>Bladder outflow obstruction</td>
<td>Monitor for active or occult GI bleeding</td>
</tr>
<tr>
<td>Seizures</td>
<td>Limited potential; seizures also may be due to AD itself</td>
</tr>
<tr>
<td>Asthma</td>
<td>History of asthma</td>
</tr>
</tbody>
</table>

Dosing Guidelines: Prescribe tacrine only when a caregiver can monitor patient compliance with drug administration at regular intervals.

Usual starting dose: 10 mg QID; do not increase dose for at least 6 weeks to observe potential delayed LFT elevation. Tacrine is available in 10-, 20-, 30-, and 40-mg capsules.
Dose titration: Increase to 20 mg QID if LFTs are normal and patient is tolerating therapy. Higher doses (eg, 30 to 40 mg QID) may be given at 6-week intervals unless side effects appear. It may take up to 6 months to see any benefit and if none is seen within this time, tacrine should be discontinued.

LFTs: After tacrine therapy is initiated, monitor LFTs every other week for at least the first 16 weeks, monthly for 2 months, every 3 months subsequently. The dose of tacrine should be reduced by 40 mg/d if LFTs are between three and five times the upper limit of normal (ULN). Tacrine should be discontinued if LFTs are greater than five times ULN. If treatment is stopped and restarted for any reason, resume weekly monitoring as described above.

Cholinergic Agonists

Although theoretically appealing, no commercially available drugs of this class have provided clinical utility in patients with AD. Although patients with AD taking bethanechol have shown some improvement on the MMSE, the drug must be given intracerebroventricularly because it does not cross the blood-brain barrier. Other oral agents (eg, pilocarpine) have been ineffective or have required frequent intravenous administration (eg, arecoline). A number of newer orally active cholinergic agonists are under study (Schneider and Tariot, 1994).
**Miscellaneous**

Selegiline (Eldepryl,® Somerset Pharmaceuticals, Inc; formerly known as L-deprenyl) is currently indicated for adjunctive use in Parkinson's disease to prolong the efficacy of levodopa. However, this drug has been shown to be effective in improving cognitive function and disturbed behavior (eg, anxiety, cooperation, agitation) in patients with AD (Schneider and Tariot, 1994) (Table 8).

Table 8. Overview of selegiline therapy

<table>
<thead>
<tr>
<th>Feature</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Irreversible selective inhibition of MAO-B at low doses (&lt;10 mg/d)</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Orally absorbed, extensive hepatic metabolism</td>
</tr>
<tr>
<td>Efficacy</td>
<td>↑ cognition and behavior</td>
</tr>
<tr>
<td>Safety</td>
<td>Nausea, dizziness, abdominal pain confusion, hallucinations headache, dry mouth, dyskinesia</td>
</tr>
<tr>
<td>Dosing</td>
<td>5 mg BID maximum. Higher doses ↑ side effects and do not improve efficacy</td>
</tr>
</tbody>
</table>

**Mechanism:** Selegiline is an irreversible and, at low doses (ie, ≤10 mg/d), selective inhibitor of monoamine oxidase type B (MAO-B). At

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higher doses, the drug loses its selectivity and also inhibits MAO-A. Monoamine oxidase is responsible for the breakdown of dopamine, serotonin, and norepinephrine and the B type is found primarily in the brain. Selegiline also may increase dopaminergic activity by other unknown mechanisms. Emerging evidence indicates that selegiline may retard the progression of AD by reducing oxidative stress in neurons (Schneider and Tariot, 1994).

**Pharmacokinetics:** The bioavailability of selegiline increases up to four times when the drug is taken with food. Selegiline is extensively metabolized in the liver and one metabolite has clinical activity. Data are not available regarding the pharmacokinetic fate of selegiline or its metabolite in patients with renal or hepatic impairment. It is not known if selegiline is excreted in breast milk.

**Efficacy:** Results of several randomized, placebo-controlled trials indicate that selegiline (10 mg/d) appears to impart beneficial effects on cognition and behavior in patients with AD (Schneider et al, 1994). Additional trials are needed to confirm these findings. Whether the benefit of selegiline is related to increased MAO-B activity that has been reported in AD or related to improvement in mood is not clear.

**Safety:** Safety data from controlled clinical trials is limited but nausea, dizziness, abdominal pain, confusion, hallucinations, dry mouth,
vivid dreams, dyskinesia, and headache have been reported. Selegiline has not been studied in children. Selegiline is rated as Pregnancy Category C (see Glossary).

**Warnings/Precautions/Drug Interactions:** Do not increase the dose of selegiline higher than 10 mg/d. CNS toxicity (including hyperpyrexia, severe agitation, hallucinations, and death) has occurred in some patients taking selegiline with TCAs, SSRIs, or meperidine. Hypertensive crises have occurred in patients taking selegiline and the sympathomimetic agent, ephedrine.

**Dosing Guidelines:** The dose of selegiline is 5 mg administered BID, with breakfast and lunch. Higher doses are not more effective and should be avoided to prevent side effects. In trials of AD patients, any clinical benefit was evident within a few weeks.

**SEDATIVE-HYPNOTICS**

**STIMULANTS**
OVERVIEW OF DRUG THERAPY: GENERAL PRINCIPLES

Elderly

Pregnancy/Lactation  (see Glossary for FDA definitions)

TREATMENT ALGORITHMS FOR COMMON PSYCHIATRIC DISORDERS

Alzheimer’s Disease

Because AD is a chronic, progressive disorder, by necessity, treatment approaches must be continually customized and adjusted according to the patient’s current situation. A multidisciplinary approach should involve both nonpharmacologic and pharmacologic avenues for the patient with AD and his or her family (Figure 1). Nonpharmacologic approaches include behavioral counseling (for patients and caregivers) and home safety evaluation (eg, providing living arrangements on a single level of the home to eliminate need to use stairs, enhance lighting in dark hallways to reduce disorientation, lower hot water temperature, etc).
EVALUATE patient:
Family/medical/drug history
Clinical examination
Laboratory/neurologic testing

INTERVIEW reliable family member/acquaintance

IMPLEMENT nonpharmacologic intervention:
Behavioral
Environmental
Social

INITIATE pharmacologic therapy
to restore neurotransmitter imbalance (tacrine, selegiline) or improve cognition (ergoloid mesylates)

ASSESS bothersome secondary behavioral disturbances:

Psychosis
Antipsychotics
  traditional (eg, haloperidol, thioridazine)
  atypical (eg, clozapine, risperidone)

Agitation
Antipsychotics (as above)
Anticonvulsants (eg, carbamezepine, sodium valproate)
Antimanic (eg, lithium)
Anxiolytics (eg, buspirone, benzodiazipines)
Antidepressants (eg, SSRIs, trazodone, nortriptyline)

Depression
Antidepressants (as above)

MONITOR therapeutic benefit, tolerability
ADJUST dose if needed

REEVALUATE
benefit and need for continued drug therapy
need to change therapeutic approach for emergence of new symptoms

Figure 1. Treatment approach to the patient with AD.
Pharmacotherapy cannot delay or prevent the onset of AD but can be directed at restoring primary underlying neurotransmitter deficits (i.e., low central ACH levels). Currently, only tacrine (see Page 19) is indicated in the US for the treatment of the dementia of AD. Ergoloid mesylates (see Page 18) have been used in elderly demented patients but with little clinical success. A number of new compounds are actively being studied (Schneider and Tariot, 1994; Schneider, 1996).

Pharmacotherapy for patients with AD also can be directed at managing secondary behavioral disturbances such as aggression or agitation, depression, or psychosis (Tables 9 and 10) (Raskind, 1995).
Table 9. Secondary behavioral symptoms of AD and the expected response to drug therapy (Sky and Grossberg, 1994)

<table>
<thead>
<tr>
<th>More likely to respond:</th>
<th>Nonspecific hyperactivity, physical or verbal agitation, classic psychoses or delusions, depressive symptoms, hallucinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less likely to respond:</td>
<td>Wandering, public disrobing, hoarding or hiding objects and possessions, repetitive questioning, social inappropriateness</td>
</tr>
</tbody>
</table>

Antipsychotics: Data supporting the use of antipsychotics and antidepressants in patients with AD are limited; much of the data have been extrapolated from studies in younger, demented patients. More trials are needed in elderly patients with strictly defined AD.

Antipsychotics have demonstrated limited efficacy and only a marginal benefit over placebo in AD (Table 10) (Raskind, 1995; Schneider et al, 1990). According to a meta-analysis, no antipsychotic drug offers substantial clinical advantage over another. Antipsychotics are most effective for managing classic psychotic symptoms (eg, grandiose, complex delusions) and less effective in patients who are not agitated, hyperactive, or not experiencing hallucinations or delusions (Raskind, 1993).
Table 10. Pharmacotherapy of behavioral disturbances in patients with AD (Raskind, 1993; Schneider and Tariot, 1994; Sky and Grossberg, 1994; Tariot, 1996)

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Behavioral features</th>
<th>Typical regimen</th>
<th>Cautions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotic</td>
<td>Symptoms resembling classic psychosis (eg, hyperactivity, grandiose or complex hallucinations, delusions)</td>
<td>Haloperidol 1 mg, thioridazine 20 mg; ↑ dose every 3 days as tolerated until therapeutic effect. Divide higher doses (eg, haloperidol up to 4.6 mg/d or thioridazine up to 150 mg/d) BID or TID. Discontinue (taper) regimen after 3 months to avoid long-term drug exposure and EPS</td>
<td>EPS more common with high-potency drugs (eg, haloperidol) whereas anticholinergic effects (eg, urinary retention, constipation, dry mouth, blurry vision, sedation, orthostatic hypotension, delirium) more common with low-potency drugs (eg, thioridazine)</td>
<td>Only marginal benefit vs placebo. Most effective in those with classic psychotic symptoms. Excess sedation and EPS limit clinical utility. Emerging data with clozapine and risperidone.</td>
</tr>
<tr>
<td>Serotonergic</td>
<td>Symptoms resembling classic psychosis (eg, hyperactivity, hallucinations, delusions)</td>
<td>Trazodone 25 to 400 mg/d (divided)</td>
<td>Trazodone: orthostatic hypotension, sedation</td>
<td>Uncontrolled, anecdotal data</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>------------------------------------</td>
<td>---------------------------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Buspirone 10 to 45 mg/d (divided)</td>
<td>Buspirone: dizziness, sedation, headache</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Anxiety, agitation, wandering, restlessness</td>
<td>Use low dose of a short- or intermediate-acting agent with inactive metabolites (eg, oxazepam 20 to 80 mg/d, lorazepam, 1 to 1.5 mg/d)</td>
<td>Tolerance or dependence with chronic use, ataxia, sedation, impaired cognition, confusion</td>
<td>No large, well controlled studies</td>
</tr>
<tr>
<td>Antimanic drugs</td>
<td>Violent behavior, impulsiveness</td>
<td>Carbamazepine 50 to 100 mg BID (up to 1000 mg/d maintenance)</td>
<td>Carbamazepine: sedation, ataxia, leukopenia, skin rash, hepatotoxicity</td>
<td>Controlled data needed; therapeutic serum level monitoring must be implemented</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------------------</td>
<td>-------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>---------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sodium valproate plasma levels of 30 to 90 μg/mL reported beneficial</td>
<td>Lithium: EPS, confusion, ataxia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lithium 250 to 1200 mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Apathy, sleep or appetite changes, psychomotor agitation or retardation</td>
<td>Select agent with low anticholinergic activity (eg. SSRI, trazodone, secondary amine)</td>
<td></td>
<td>Very limited controlled clinical trial data</td>
</tr>
<tr>
<td>Blockers</td>
<td>Agitation, hostility</td>
<td>Propranolol 40 to 520 mg/d (divided)</td>
<td>Use with caution in heart failure, obstructive pulmonary disease, asthma, diabetes, hyperthyroidism; drug interactions common</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Pindolol 60 to 100 mg/d (divided)</td>
<td></td>
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</tr>
</tbody>
</table>


Because functional improvements are often limited by excess sedation and substantial EPS, clinicians should consider the impact of drug therapy on the quality of life of the AD patient and their caregivers. If the patient and caregiver can tolerate certain disruptive behavior, antipsychotic drug therapy could be withheld, at least temporarily. On the other hand, however, some evidence indicates that psychotic symptoms may be associated with faster cognitive deterioration (Raskind, 1995). Thus, outcome trials are needed to determine usefulness of antipsychotic drugs in patients with AD.

**Antidepressants:** Antidepressants have not been well studied in depressed patients with AD and the response to placebo is very high (Table 10) (Alexopoulos, 1996). Thus, early "response" to an antidepressant may forecast an early "relapse." These drugs may improve mood or disturbed sleep-wake cycles but have no effect on cognitive functioning. Clinicians should select a low dose of an antidepressant with few anticholinergic properties such as an SSRI, a secondary amine (e.g., nortriptyline, desipramine) and increase the dose gradually. If improvement is not noted, select another agent. Some evidence indicates that plasma levels considered therapeutic in nondemented depressed individuals may not apply to demented depressed patients (Alexopoulos, 1996).
MENTAL HEALTH ORGANIZATIONS

Alzheimer’s Disease (Cohen, 1995)

Alzheimer’s Association (AA)

70 E Lake Street, Chicago, IL 60601

TEL: 312-853-3060 or 800-272-3900

National organization with extensive family-oriented information and newsletter. Local chapters are an excellent resource for information on community services (eg, adult day care, respite programs).

American Association of Retired Persons (AARP)

TEL: 800-424-3410

Provides literature on services and programs for older adults.

Area Agency on Aging

TEL: Check local listing for nearest Area Agency on Aging.

Division of the US Department of Health and Human Services; coordinates a large network of offices on aging to provide information and referrals.
Alzheimer’s Disease Education and Referral Program (ADEAR)

TEL: 800-438-4380.

Sponsored by the National Institute on Aging. ADEAR performs free literature searches for clinicians and researchers on AD.

Alzheimer’s Disease Centers (ADC)

Offers diagnosis and management services (costs are variable), information about AD and local resources, opportunities to participate in drug trials. Contact ADEAR (above) for nearest center.

PATIENT ADVOCACY GROUPS

PUBLICATIONS

INTERNET RESOURCES
ACH: acetylcholine.

AD: Alzheimer’s disease.

ADAS cog:

BID: twice daily.

ChAT: choline acetyltransferase.

CNS: central nervous system.

CT: computed tomography.

Cytochrome P450 system (CYP450): Proteins that catalyze oxidative drug metabolism. Many families and subfamilies of isoenzymes. Cytochromes (CYP) IA2, IIC, IID6, and IIIA4 are relevant to metabolism of many psychotherapeutic agents and clinically important drug interactions.

EPS: Extrapyramidal side effects; common with antipsychotic therapy. Includes acute dystonic reactions (eg, facial grimacing, oculogyric crisis), akathisia (ie, subjective feeling of restlessness), pseudoparkinson features (eg, slowed movement, masked facies, rigidity, resting tremor) and tardive dyskinesia (ie, irregular facial movements). EPS are treatable with antiparkinsonian drugs.

GABA: gamma aminobutyric acid.

GI: gastrointestinal.

HIV: human immunodeficiency virus.
LFTs: liver function tests such as alanine aminotransferase (ALT [formerly SGPT]), aspartate aminotransferase (AST [formerly SGOT]), gamma-glutamyl transpeptidase (GGT), bilirubin.

MAOI: monoamine oxidase inhibitor.

MMSE: Mini Mental State Examination: a short (<10 minutes to administer), structured (11 questions) clinician-administered examination of cognitive aspects of mental function (Folstein et al, 1975). Good for initial and serial measurement of mental function; reliable over time.

MRI: magnetic resonance imaging.

Neuritic plaques: also called senile plaques. Like NFT, a hallmark neurohistologic feature of AD. Neuritic plaques have a central core of insoluble β amyloid protein surrounded by distended and abnormal dendrites and small axons.

NFT: neurofibrillary tangles. A neurohistologic feature of AD consisting of filament bundles in cell bodies, axons, dendrites found in the cerebral cortex and hippocampus. NFT density closely correlated with degree of cognitive impairment.

NSAID: nonsteroidal anti-inflammatory drug (eg, ibuprofen, indomethacin, naproxen, etc).

PET: positron emission tomography.

Pregnancy Categories: The Food and Drug Administration has established five categories for classifying drugs for use during pregnancy.
Category A: Adequate studies in pregnant women have not
demonstrated fetal risk in the first trimester and there is no
evidence of risk in later trimesters.

Category B: No fetal risk in animal studies but no adequate
studies in pregnant women. OR, animal studies have shown adverse
effect but adequate studies in pregnant women have not
demonstrated fetal risk during the first trimester and no evidence
of risk in later trimesters.

Category C: No adverse effect in animal studies but no adequate
studies in humans. Benefits from use of the drug by pregnant
woman may be acceptable despite these risks. OR, no animal
reproduction studies and no adequate studies in humans.

Category D: Evidence of human fetal risk but potential benefits
from the drug in a pregnant women may be acceptable despite these
risks.

Category X: Studies in animals or humans demonstrate fetal
abnormalities or evidence of fetal risk; the risk of use clearly
outweighs any possible benefit.

QID: four times daily.

SPECT: single positron emission computed tomography.

SSRI: selective serotonin reuptake inhibitor. Class of antidepressants
includes fluoxetine, paroxetine, sertraline.

TCA: tricyclic antidepressant.

TID: three times daily.


OPTIONAL; need decision regarding its inclusion after review of Draft I.
ATTACHMENT E
February 4, 1997

Charles B. Nemeroff, MD, PhD  
Professor and Chairman  
Dept of Psychiatry and Behavioral Sciences  
Emory University School of Medicine  
PO Drawer AF  
Atlanta, GA 30322-4990

RE: PRIMARY CARE HANDBOOK OF PSYCHOPHARMACOLOGY

Dear Charlie:

I am pleased to provide an update on the status of this project. We have begun development of the text, and Diane Coniglio, PharmD is the primary technical writer and project manager. I will be working closely with Diane at all times and will serve as technical editor. You and Alan are in good hands with Diane; she has many years of experience and is a creative and accomplished technical writer.

We have developed a timeline for completion of work as follows:

- Sample text for preliminary comment  Feb 21
- Draft I to co-authors/APPI/sponsor  May 2
- Comments to STI  May 30
- Draft II to co-authors/sponsor  June 20
- Comments to STI  July 11
- Draft III to co-authors/sponsor for sign-off  July 25
- Production begins  August 1
- Page proofs to co-authors/APPI/sponsor for final approval  August 15
- Disk to publisher for printing  September 1

A complete content outline is enclosed for your comment. We have made several key content assumptions as listed below. Please comment on these issues.

1. Investigational drugs will not be discussed
2. Only oral formulations will be discussed
3. Somatization disorder and general treatment guidelines for elderly and pregnant/lactating patients have been added. OK?
4. The benzodiazepine-, antipsychotic-, and barbiturate-classes contain many drugs. Should we select representative agents from each of these classes rather than discussing the entire class?
5. Should thyroid hormone augmentation of resistant depression be included or is this an issue not commonly encountered in primary care?

WB 193608

505 Morris Avenue, Springfield NJ 07081 • Telephone: (201) 376-5655 • Fax: (201) 376-0611 or (201) 376-5567
I hope that our progress to date meets with your approval. Diane Coniglio will be in touch with you in the near future to discuss the issues addressed in this letter and to gain the benefit of your input. In the meantime, please do not hesitate to call me if you have questions or require additional information.

Sincerely,

Sally Laden, MS
Associate Editorial Director

encl

cc: C Reinburg
    B Brand
    J Armson
    J Romankiewicz
    M Philips
    D Coniglio
    J Leib
    .1112

WB 193609
Note: The authors have worked to ensure that all information in this book concerning drug dosages, schedules, and routes of administration is accurate as of the time of publication and consistent with standards set by the U.S. Food and Drug Administration and the general medical community. As medical research and practice advance, however, therapeutic standards may change. For this reason and because human and mechanical errors sometimes occur, we recommend that readers follow the advice of a physician who is directly involved in their care or the care of a member of their family.

Books published by the American Psychiatric Press, Inc., represent the views and opinions of the individual authors and do not necessarily represent the policies and opinions of the Press or the American Psychiatric Association.

This text reviews the use of pharmacologic agents, not all of which are cleared for marketing by the FDA for the psychiatric disorders discussed in this publication.

In keeping with good clinical practice, before prescribing any medication, review the complete prescribing information, including indications, contraindications, warnings, precautions, and adverse effects.

First Edition
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02 01 00 99 4 3 2 1
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Manufactured in the United States of America on acid-free paper

American Psychiatric Press, Inc.
1400 K Street, NW
Washington, DC 20005
www.appi.org

Library of Congress Cataloging-in-Publication Data
Nemeroff, Charles B.
p. cm.
Includes bibliographical references and index.
ISBN 0-88048-990-1
1. Mental illness—Treatment Handbooks, manuals, etc.
2. Psychopharmacology Handbooks, manuals, etc. 3. Primary care (Medicine) Handbooks, manuals, etc. 4. Schatzberg, Alan F. II. Title.
DNLM: 1. Mental Disorders—drug therapy Handbooks. 2. Mental Disorders—diagnosis Handbooks. 3. Psychotropic Drugs Handbooks.
WM 34 N435r 1999)
RC454.4.N46 1999
G168.9'3—dc21
DNLM/DLC
for Library of Congress
99-15420

British Library Cataloguing in Publication Data
A CIP record is available from the British Library.
Mental health is an important public health issue, as evidenced by the prevalence of psychiatric problems that are associated with tremendous disability, immense personal suffering, and a heavy economic burden. National survey data indicate that 48% of a representative US adult sample population have reported a psychiatric disorder at one time or another and that about 30% have reported a disorder during the past 12 months. Less than half of those with a lifetime history of a psychiatric disorder ever received treatment. Interestingly, 14% of the sample reported a lifetime history of three or more comorbid psychiatric disorders. These findings speak directly to the importance of screening, identifying, and treating patients with mental illness.

The primary care setting has been called a de facto mental healthcare system in the US and the hidden mental health network. About 60% of patients with a psychiatric disorder are identified and receive treatment in a primary care setting. With the changing healthcare environment in the US, more and more patients are entering the primary care network, creating ever larger, busier, and more closely regulated practices. Thus, primary care physicians are being forced to develop or refine strategies for screening and identifying patients with psychiatric disorders.

This handbook, Recognition and Treatment of Psychiatric Disorders: A Psychopharmacology Handbook for Primary Care, was developed to address these issues and meet some of these needs. Another factor that led to the development of this handbook is the continually growing number of new drugs being introduced for the treatment of mental disorders and of currently available drugs being used for new psychiatric indications. Although many psychiatric disorders are suitable for treatment in the primary care setting, issues for referral to psychiatric colleagues are germane to contemporary practice and are discussed in this text. We recognize that primary care physicians have little extra time to read the voluminous psychiatric literature and distill it down to practical yet timely and accurate treatment strategies, and we hope this handbook will aid in that endeavor.

We thank SmithKline Beecham Pharmaceuticals for providing an unrestricted educational grant to Scientific Therapeutics Information, Inc, for the development of this handbook. The editorial assistance of Diane M. Coniglio, PharmD, and the staff of Scientific Therapeutics Information, Inc, is gratefully acknowledged. We also appreciate the support of our publisher, American Psychiatric Press, Inc.

Charles B. Nemeroff, MD, PhD

Alan F. Schatzberg, MD

Preface
ATTACHMENT G
Hi Kim,

Attached please find the poster to be presented at US Psych Congress. Please provide feedback.

Regards,
Kevin

- Poster_USPSYCHCONGRESS(Patient_Satisfaction).doc

Attachments: Poster_USPSYCHCONGRESS(Patient_Satisfaction).doc; embedded picture.bmp; embedded picture.bmp; embedded picture.bmp; embedded picture.bmp; embedded picture.bmp; embedded picture.bmp; embedded picture.bmp
ATTACHMENT H
PAROXETINE TREATMENT OF MOOD DISORDERS IN WOMEN:
PREMENSTRUAL DYSPHORIC DISORDER AND HOT FLASHES

Authored by:
Kimberly A. Yonkers, MD
Associate Professor of Psychiatry
Yale University School of Medicine
New Haven, CT

For submission as part of a supplement to:
Psychopharmacology Bulletin

Prepared by:
C. Gloria Mao, PharmD
Sally K. Laden, RPh, MS
Scientific Therapeutics Information, Inc
Springfield, New Jersey

Draft I
March 24, 2003
ATTACHMENT I
Advancing the Treatment of Mood and Anxiety Disorders:
The First 10 Years’ Experience with Paroxetine

Introduction
By Charles B. Nemeroff, MD, PhD

Neuropharmacology of Paroxetine
By Michael J. Owens, PhD, and Charles B. Nemeroff, MD, PhD

In Vivo Neuroimaging Correlates of the Efficacy of Paroxetine in the Treatment of Mood and Anxiety Disorders
By Clinton Kilts, PhD

Pharmacokinetics, Drug Interactions, and Tolerability of Paroxetine and Paroxetine CR
By C. Lindsay DeVane, PharmD

Paroxetine Treatment of Major Depressive Disorder
By Martin B. Keller, MD

Treatment of Panic Disorder: Focus on Paroxetine
By Mark H. Pollack, MD, and Alicia C. Doyle, BA

Paroxetine Treatment of Generalized Anxiety Disorder
By David V. Sheehan, MD, MBA, and C. Gloria Mao, PharmD

Treatment of Posttraumatic Stress Disorder: The Impact of Paroxetine
By Jonathan R. T. Davidson, MD

Obsessive-Compulsive Disorder: Implications of the Efficacy of an SSRI, Paroxetine
By Philip T. Yonan, MD

Advances in Recognition and Treatment of Social Anxiety Disorder: A 10-Year Retrospective
By Murray B. Stein, MD, FRCPC

Paroxetine Use in Medically Ill Patients
By Steven Strot, MD, PhD, Wendy I. Somerst, MD, Andrew Miller, MD, and Dominique L. Museliman, MD, MS

Paroxetine Treatment of Depression in Late Life
By Charles F. Reynolds III, MD

Paroxetine Treatment of Mood Disorders in Women: Premenstrual Dysphoric Disorder and Hot Flashes
By Kimberly A. Yonkers, MD

Clinical Management of Perinatal Depression: Focus on Paroxetine
By D. Jeffrey Newport, MD, MSCR, MDit, and Zachary N. Stowe, MD

Paroxetine Treatment of Mood and Anxiety Disorders in Children and Adolescents
By Karen Dineen Wagner, MD, PhD

Efficacy and Tolerability of Controlled-Release Paroxetine
By Robert N. Golden, MD

psychopharmbulletin.com
Paroxetine Treatment of Mood Disorders in Women: Premenstrual Dysphoric Disorder and Hot Flashes

By Kimberly A. Yonkers, MD

ABSTRACT - With the relatively recent introduction of the selective serotonin reuptake inhibitor (SSRI) class of antidepressants, increased attention has been focused on the use of antidepressants in the treatment of mood disorders across the female life cycle. Evidence for the efficacy of antidepressants in the treatment of premenstrual dysphoric disorder (PMDD) and hot flashes associated with menopause and breast cancer has emerged. The clinical trials experience with paroxetine and the controlled-release (CR) formulation of paroxetine is reviewed. Psychopharmacology Bulletin. 2003;37(Suppl 1): 135-147

INTRODUCTION

Depression is one of the most significant and disabling illnesses in women. Findings from the World Health Organization's Global Burden of Disease study illustrate the relative ranking of depression as a source of death and disability worldwide and in the United States. Based on 1996 estimates, the leading cause of disability among both men and women in the United States was ischemic heart disease. Motor vehicle accidents were the second most common source of death and disability in men. In sharp contrast, the second largest contributor to disability in women was major depression, which in women was ranked higher than cerebrovascular disease, respiratory tract cancers, osteoarthritis, and breast cancer.1

For reasons that are not completely understood, women are at increased risk for mood disorders compared with men. Gender differences in the rates of major depression are not apparent in prepubertal children. However, beginning with puberty and continuing through the end of a woman's childbearing years in midlife, the ratio of major depression in females to males is 2:1.2-3 There are particular times during a woman's reproductive life, such as pregnancy, the postpartum period, the

Key Words: paroxetine, women, premenstrual dysphoric disorder, menopause, breast cancer, hot flashes

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direct comparative studies are warranted to better identify candidates for continuous vs intermittent SSRI treatment.

Findings from pilot studies also suggest that paroxetine and paroxetine CR reduce the frequency and severity of hot flashes in perimenopausal women and women with breast cancer. Again, additional studies are needed to assess the optimal duration of treatment of hot flashes, particularly in menopausal women.

DISCLOSURE

This work was supported by an unrestricted educational grant from GlaxoSmithKline. Dr. Yonkers serves as a consultant and receives grant and research support from Eli Lilly, GlaxoSmithKline, and Berlex Laboratories. She receives grant and research support from Pherin Pharmaceuticals and serves as consultant for Pfizer and Wyeth.

REFERENCES

ATTACHMENT J
Hi Sally

Would you please provide both myself and Holly White at Cohn and Wolfe copies of the proofs.

Thanks in advance

Cheers Sheila

Original Message

From: Sheila.X.Hood@sb.com@YRINC
Sent: Wednesday, February 28, 2001 3:37 PM
To: WHITE; HOLLY
Subject: Publication date for Paroxetine Adolescent Depression study (PAR 329)

Hi Holly

Do you want to receive copies of the proofs? Should we do any media around the publication?

Cheers Sheila
ATTACHMENT K
By signing below, I, James McCafferty, MS, approve Draft 11 of the manuscript entitled "Efficacy of Paroxetine in the Treatment of Adolescent Major Depression: A Randomized, Controlled Trial" dated November 3, 2000, and agree that it can be released to Martin Keller, MD to submit for publication to *Journal of the American Academy of Child and Adolescent Psychiatry*. I understand that all copyrights to the article, once published, belong to the publisher and not to myself, STI, or SmithKline Beecham Pharmaceuticals.

**PLEASE CHECK THE APPROPRIATE BOX:**

- [ ] Manuscript approved without changes.
- [ ] Manuscript approved with changes indicated; no additional draft needed.
- [ ] Manuscript not approved; changes indicated, and additional draft required for approval.

Signature ___________________________________________ Date _____________.

.1301