<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOOK REVIEW</td>
<td>442</td>
</tr>
<tr>
<td>Stephanie M. Buscini</td>
<td></td>
</tr>
<tr>
<td>INTRODUCTION: DEPRESSION—A TREATABLE PUBLIC HEALTH PROBLEM: THE ROLE FOR PHARMACISTS IN OPTIMIZING PATIENT OUTCOME</td>
<td>444</td>
</tr>
<tr>
<td>Patricia A. Marken</td>
<td></td>
</tr>
<tr>
<td>TOOLS AND TECHNIQUES FOR EVALUATING DEPRESSION</td>
<td>448</td>
</tr>
<tr>
<td>Jessica S. Wehner and Steven C. Stoner</td>
<td></td>
</tr>
<tr>
<td>DEFINING RESPONSE AND ATTAINING THERAPEUTIC GOALS FOR DEPRESSION</td>
<td>453</td>
</tr>
<tr>
<td>Naomi A. House and Roger W. Sommi, Jr.</td>
<td></td>
</tr>
<tr>
<td>ANTIDEPRESSANTS: USING PHARMACOLOGY TO INDIVIDUALIZE THERAPY</td>
<td>458</td>
</tr>
<tr>
<td>Daniel J. Dugan</td>
<td></td>
</tr>
<tr>
<td>ANTIDEPRESSANT DRUG INTERACTIONS</td>
<td>467</td>
</tr>
<tr>
<td>Sheila R. Botts and Cara Alfaro</td>
<td></td>
</tr>
<tr>
<td>STRATEGIES FOR TREATMENT REFRACTORY DEPRESSION</td>
<td>478</td>
</tr>
<tr>
<td>Jessica L. Goren</td>
<td></td>
</tr>
<tr>
<td>MANAGEMENT OF DEPRESSION IN CHILDREN AND ADOLESCENTS</td>
<td>488</td>
</tr>
<tr>
<td>Julie A. Dopheide</td>
<td></td>
</tr>
<tr>
<td>GERIATRIC DEPRESSION</td>
<td>498</td>
</tr>
<tr>
<td>Stephen C. Cooke and Melissa L. Tucker</td>
<td></td>
</tr>
<tr>
<td>DEPRESSION IN WOMEN ACROSS THE LIFE CYCLE</td>
<td>511</td>
</tr>
<tr>
<td>Thea R. Moore and Angela M. Emanuel</td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>Authors</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>MANAGEMENT OF DEPRESSION IN PATIENTS WITH COMORBID CARDIOVASCULAR DISEASE</td>
<td>Leigh Anne Nelson and Joy R. Abu-Shanab</td>
</tr>
<tr>
<td>DEPRESSION AMONG PATIENTS WITH HIV/AIDS: A TREATMENT DILEMMA</td>
<td>Gerald P. Overman and Stacey L. Anderson</td>
</tr>
<tr>
<td>CONSIDERATIONS FOR THE USE OF ALTERNATIVE THERAPIES IN THE TREATMENT OF DEPRESSION</td>
<td>Angela M. Emanuel, Thea R. Moore, and Patty Ghazvini</td>
</tr>
<tr>
<td>INDEX</td>
<td></td>
</tr>
</tbody>
</table>
EDITORIAL STATEMENT

The objective of the editorial board of the *Journal of Pharmacy Practice (JPP)*, as well as that of Sage Publications, is to offer the practicing pharmacist topical, important, and useful information to support pharmacy practice and pharmaceutical care and expand the pharmacist's professional horizons.

The *Journal of Pharmacy Practice* is presented in a single-topic, scholarly review format. Guest editors are selected for particular expertise in the subject area; they then recruit contributors from that practice or topic area and bring the information together in a relevant and timely fashion for the pharmacist reader.

The readership, like the profession, is diverse, and so are the topics. Since the walls between practice sites have all but disappeared, each practitioner needs to be informed of developments, and basics, of a wide variety of topics. By focusing on a single topic each issue, the journal provides the reader with a thorough review of that topic written by experienced and accomplished practitioners in that topic area. Practice issues, practice settings, therapeutics issues, disease management, research, government, legal, and regulatory issues are reviewed in a timely manner. The reader is advised of several forthcoming topic issues.

Established in 1988, the *Journal of Pharmacy Practice* is published 6 times per year. In addition to the main topic review articles, each issue will contain an Adverse Drug Experience Report that will address a clinically relevant adverse reaction, including a review of the pertinent literature about the mechanism and experience with that reaction. It will also include commentary and advice for the prevention of that adverse drug experience through the provision of complete pharmaceutical care. From time to time, special articles identified as Contemporary Practice Issues will also be presented.

We intend that the *Journal of Pharmacy Practice* will be of practical value to you. It has been used in daily practice as a reference, it saves time in literature review, and provides a consolidated source of information and opinion for topics that affect the profession of pharmacy and the patients that pharmacists serve. Each issue will thoroughly review a topic, providing a validating experience for the reader who is familiar with the topic and education for the reader who is not (validating for the expert, educating for the novice).

Every effort has been made to check generic and trade names and to verify drug doses. The ultimate responsibility, however, lies with the practitioner. Please convey any errors or comments to the Editor.

Unsolicited manuscripts will be considered and used if appropriate for a specific and timely single topic issue or contemporary practice issue, and adverse drug experience reports will be considered and published on a space-available basis.
will publish in future issues . . .

Oncology Therapeutics
Frontiers in Pharmacotherapy
Critical Care Medicine
Upper Gastrointestinal Disorders
Hepatology and Lower Gastrointestinal Disorders
Cardiovascular Pharmacotherapy
Nephrology
Sports Medicine
Space Physiology and Pharmacology
The profession of pharmacy is constantly growing and adapting to the changing needs of the health care environment. In this transformation, tools such as the Internet supply pharmacists with a plethora of information in seconds. However, with hundreds of “pharmacy” Web sites being launched on a seemingly daily basis, we must be able to distinguish those of value from those that are just trying to sell a product. The United States Pharmacopeial Convention Inc. located at www.usp.org (contact webmaster@usp.org) will be reviewed below.

The United States Pharmacopeia (USP), a not-for-profit and nongovernmental organization, is a world-recognized entity that establishes drug standards. As the role of pharmacy has grown, so has the role of the USP. In addition to its nationally and internationally accepted drug standards, the USP operates two medication error programs, Medication Errors Reporting and MedMARx™. It establishes standards for dietary supplements and standards for veterinary medicine. The USP is an invaluable source of information for consumers and health care providers. MICROMEDEX, a division of Thomson Publishing, is now producing the USP DI® database, which includes nearly all Canadian and U.S. medications as well as uses (approved, “off-label,” and investigational).

The Web site’s home page is well organized. The links are visibly marked, and the various services and different areas of the Web site are clearly delineated. There is no bombardment of flashing sponsor banners or anything of that nature. On the contrary, there are no visible advertisements other than the products and services offered by the USP.

The Web site allows for easy and quick use. A highlighted navigation bar at the top of the page lists several sections of the Web site. There is a direct link to a Support section, which allows for troubleshooting on USP software. There is a Calendar of Events section that publicizes upcoming meetings and conventions related to the USP and in other pharmaceutical areas. A well-structured list of various topic headings is presented on the Links page. All of the Web sites are not randomly and immediately displayed. Only when clicking on the topic of interest do you view an in-depth listing of useful Web sites that are current and in progress. There is a Contact USP section that lists the contact names, addresses, phone numbers, and/or e-mail addresses and Web sites of individuals and organizations. Listed contacts include where to direct monograph questions or obtain product and service information. The News Releases section is updated almost daily. It contains recent press releases from the USP, for example, when a new chairman is elected or when the organization sponsors certain projects. Larger articles of interest are available for free download using Adobe Acrobat®.

The Contents portion allows direct access to services provided at the Web site. The About USP section provides access to news and resources concerning the USP and its services. The Drug Standard section and the Drug Information section provide breaking news on material, including standardization and quality control procedures, updates in drug monographs, and interesting patient information. The Dietary Supplement section has information for consumers about herbal and dietary supplements. It contains articles on what consumers should look for when shopping for supplements. Also available are progress notes on achieving standardized monographs for herbal supplements including uses, recommended doses, and side effects. Some completed monographs are available for viewing. The Practitioner Reporting area is one of the best features of the USP Web site. Here, pharmacists and other health care providers can report medication errors. The reporting can be done online or by downloading a printable form. In addition, summaries of past error reports, lists of common errors, and guidelines for avoiding errors are available for downloading. The Veterinary Medicine area of the Web site contains various veterinary links, information, and resources. Finally, there is a USP Product section, which allows for purchasing of USP books, software, and services, and a USP Volunteer section, which allows for feedback from those currently involved in USP programs.

As more pharmacists look to the Internet for dispensing or reference tools, the USP Web site will be important enough to bookmark. It is a well-organized, up-to-date Web site that can be quite useful to pharmacists and consumers alike. The error reporting is simplified, and the Dietary Supplement section (although not complete) looks promising. The links to
other pharmacy Web sites are also current and functional. Although the site is an excellent source of information, it does not replace actually having USP software or reference guides. There is no login required to access the Web site; however, references and standards are not free. Several payment preferences and corporate account setup options are available.

Stephanie M. Bascini, RPh, PharmD student, St. John’s University, College of Pharmacy and Allied Health Sciences, Jamaica, New York.
Depression—A Treatable Public Health Problem: The Role for Pharmacists in Optimizing Patient Outcome

Depression is common, with epidemiological studies suggesting a lifetime prevalence of about 17%. Depression is also one of the most costly and devastating illnesses to mankind, despite advances in treatment and significant efforts in educating health care providers about recognition and appropriate treatment. These efforts include the DART (Depression Awareness Recognition and Treatment) program from the National Institute of Mental Health (NIMH), thousands of continuing education conferences for physicians and pharmacists and numerous well-written and widely disseminated practice guidelines on depression.

The significant impact of depression on patients and their families is highlighted by a finding from the World Health Organization that rated the relative cost of depression as among the highest of 107 illnesses and injuries using a technique called Disability Adjusted Life Years (DALYs). A DALY is calculated disease burden on life years lost and years living with disability. Evidence published in the early 1990s demonstrated clearly that depression is as costly to the economy as cardiovascular disorders and cancer. In addition, functioning and well-being was comparable to or worse than in patients with hypertension, diabetes, rheumatoid arthritis, advanced coronary heart disease, angina, back problems, COPD, or asthma. Depression is expensive in its own right, but it also increases the costs of providing general medical care. A study comparing the general medical costs in an HMO, in depressed and nondepressed patients, found that depressed patients were more than 1.5 times as expensive per year to care for and that specialty medical care only accounted for up to 20% of the difference.

The long-term consequences of depression and the chronic nature of the illness in many people have only recently been understood. Depression contributes significantly to premature death through suicide and poorer outcome if associated with a general medical condition. For example, depression in the post-myocardial-infarction period increases the risk of death over the next year almost 4-fold. Unemployment, absenteeism, decreased productivity, and interpersonal problems at work are a common consequence of depression, and improvement in these symptoms often lags behind improvement in the clinical features of the illness.

When chronic depression starts at an early age, there is a significant impact on a person’s ability to accumulate “human capital” or advanced education that increases occupational choice and earnings potential. For example, when a woman experiences depression before age 22, she has equal employment...
rates as compared to those who develop depression later in life, but her income over her lifespan is significantly less. Fortunately, response to treatment is independent of age of onset, highlighting the need for vigorous and early treatment to minimize the impact on a person’s long-term quality of life.9

This information, in its totality, paints a bleak picture of the impact of depression on individuals and society. Fortunately, effective treatment is available, even if significant gaps continue to exist between the efficacy and effectiveness of these strategies. Pharmacists can play a pivotal role in detecting depression and ensuring that adequate treatment is implemented and followed. Most people with depression are treated in an outpatient setting and through primary care services. Detection of depression remains a very important problem because of ongoing stigmatization, patients being unclear with physicians about their symptoms, the lack of public understanding about the disease and treatment options, and noncompliance once treatment is implemented. Many of these issues can be addressed by pharmacists who are positioned to identify changes in patient status, educate patients on the role of medication in their overall management and monitor for response and compliance.

The purpose of this journal is to provide comprehensive and relevant information for pharmacy practitioners in the proper identification and care of people with depression.

Drs. Wehner and Stoner will provide an overview on how to evaluate depression including clinical interview techniques, common rating skills and their interpretation and a perspective on appropriate follow-up care to ensure an optimal outcome. Dr. Dugan will discuss the pharmacology antidepressants and how to use this knowledge in making choices that are individualized to patients needs.

Depression is an illness that requires months of treatment, even for patients with a single episode. Clinicians need a clear understanding of the term’s response, resolution, remission, recovery, and prevention if they are to adequately monitor depression once treatment has been initiated. Drs. House and Sommi will present accepted definitions for these terms along with dosing strategies and considerations when determining duration of treatment to ensure an optimal therapeutic response.

Despite our best efforts, treatment will sometimes fail. Dr. Goren will discuss reasons for treatment failure and ways to evaluate whether a patient has a true case of refractory depression and what steps can be taken before less proven therapies are implemented. She will also discuss treatment options for those patients who are truly a partial responder or are refractory to standard therapies.

Managing drug interactions between antidepressants and other medications is an important aspect of care for depressed patients, especially because many have comorbid medical conditions requiring medications. Antidepressants vary widely in their ability to produce significant drug interactions. Drs. Botts and Alfaro will discuss the relative differences between the antidepressants with respect to drug interactions, with a focus on interactions that are clinically relevant.

Even though depression occurs in all age groups, the specifics of identifying and treating depression in pediatric and adolescent patients have been poorly understood. Clinical trials to identify the best strategies for managing depression in children and adults have increased, especially since the Food and Drug Administration has mandated studies in children and the NIMH has been a strong advocate for this research. Dr. Dopheide will discuss treatment strategies for pediatrics.

At the other end of the life spectrum is depression in the elderly, a condition historically ignored as it was considered to be a part of normal aging. Depression is not a normal part of aging, and elderly people with depression can have a robust response to treatment. However, drug selection is a more complex issue in the elderly because of their comorbid medical conditions and an increased risk of drug interactions and adverse effects. Drs. Cooke and Tucker will discuss strategies to optimize depression management in the elderly.
Women are particularly vulnerable to depression and experience the disease at twice the frequency of men. Women are at risk for developing depression when they are pregnant, during the postpartum period and also in the perimenopausal and postmenopausal periods. Treatment selection issues across a woman’s lifespan, along with the most recent information surrounding differential response in women will be discussed by Drs. Moore and Emanuel.

Depression in the medically ill is a particularly difficult problem. Identification may be more difficult as the sensitivity to depressive symptoms such as fatigue, weight loss and insomnia may be less when they are also symptoms of the patient’s medical condition. Additionally, depression in the seriously medically ill may be written off as expected or normal reactions to change in health status and not an independent condition. Drs. Nelson and Abu-Shanab will discuss the identification and treatment strategies for people with depression and cardiovascular disease. Drs. Overman and Anderson will address these issues in patients with HIV/AIDS.

Alternative medications are commonly used in treating depression, and in one study, they were found to be used more commonly than conventional treatments. Pharmacists are obligated to understand the potential benefits and risks of alternative medicine in treating depression, along with the pharmacology, dosing strategies and drug interactions of the agents used most commonly by our patients. Dr. Emanuel et al. will discuss the role of alternative medicines and natural products and management of depression.

Despite our best efforts, about 20%–30% of patients do not have an adequate response to antidepressants. The availability of new antidepressants since the release of fluoxetine in 1987 has expanded, but there has not been a truly different pharmacological approach to treating depression in decades. Many agents that use a different path to the resolution of depressive symptoms are under investigation. Also, improved models of care have been proposed to ensure that we close the gap between effectiveness. Dr. Rappa et al. will discuss these issues and give practitioners a look to the future as to what we may see to improve patient care.

A special note of thanks is extended to the contributing editors, Dr. Gary Levin of the University of Florida and Dr. Steven Stoner of the University of Missouri–Kansas City, without whose expertise this issue of the journal would not be possible.

It is our hope as authors in this issue of the journal that the readers will come away with a better understanding of the importance of depression as a cause of morbidity and mortality in this country and with an understanding as to how they, as practicing pharmacists, can make a difference in the lives of their patients.

REFERENCES


*Patricia A. Marken*
PharmD, FCCP, BCPP, Chair and Associate Professor of Pharmacy Practice
Associate Professor of Psychiatry
University of Missouri–Kansas City
Schools of Pharmacy and Medicine
2411 Holmes M3-C19
Kansas City, MO 64108
Tools and Techniques for Evaluating Depression

Jessica S. Wehner and Steven C. Stoner

Depression is a common and under-recognized disease state usually treated in the outpatient setting. Since it does not usually require sophisticated laboratory tests or physical evaluations as a component of monitoring, depression is a condition that can be managed by pharmacists in any setting. Due to depression’s high prevalence, pharmacists must be aware of the usual presentation so they can better identify patients in need of treatment. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) describes specific criteria needed for the diagnosis of depression to be made. The diagnostic criteria in DSM-IV are essentially the target symptoms used to monitor changes in a patient’s status. Psychometric rating scales assess the severity of psychiatric symptoms in a standardized manner. Several rating scales are currently available to assess depression, including the Hamilton Rating Scale for Depression, Montgomery-Asberg Depression Rating Scale, Beck Depression Inventory and Zung Self-Rating Scale. Rating scales can help pharmacists assess a change in symptoms or determine the baseline severity of symptoms. They also provide a framework to gather information from the patient. By understanding the presentation of depression and simple ways to assess it, pharmacists can be proactive in treating this common and sometimes life-threatening psychiatric disorder.

KEY WORDS: assessment, evaluation, depression, rating scales.

INTRODUCTION

Depression is a common and often debilitating medical disorder that creates physical and psychological impairment and decreases a person’s ability to function productively within society. The treatment of major depression focuses on a broad range of symptoms that must be identified and evaluated for their severity prior to the initiation of appropriate treatment. Surveys of outpatient medical and mental health providers confirm that primary care physicians are the major providers of depression management and not, as is the perception, inpatient specialty care. Primary care physicians account for the bulk of antidepressant prescriptions. Recent data suggest that primary care physicians only recognize 40% to 50% of patients who have current major depression. Pharmacists, due to their ready access and clinical expertise in choosing drug therapy, can contribute to the recognition and treatment of depression. They can also monitor treatment response, especially as patients return for refills of their antidepressants. With depression being a very common and under-recognized illness, pharmacists are positioned to be an important factor in its appropriate identification and treatment.

The lifetime prevalence of major depression is estimated to be 15% in women and 10% of men. In addition to the prevalence rate, it is important to recognize other factors that are associated with major depression. The Epidemiology Catchment Area Study found a gender
difference in the prevalence, with women being twice as likely to develop major depression than men. Genetics also plays a role as those with a first-degree relative affected by major depression are one to three times more likely to be affected themselves. Depression affects all age ranges, as the elderly and children are more commonly affected. Therefore, it is important that all disciplines of medicine are able to recognize the signs and symptoms of depressed patients to properly treat this common disease.

The purpose of this paper is to provide the pharmacist with tools for recognizing and monitoring depression. By reviewing the diagnostic criteria and common rating scales to assess the criteria, pharmacists will have a framework in which to work with patients in the care of their depression.

Many disease states are commonly associated with depression.

GLOBAL ASSESSMENT

The Diagnostic and Statistical Manual of Mental Disorders (4th ed., revised) (DSM-IV-R) is the official list of formal criteria that must be met in order for a psychiatric diagnosis to be made. According to the DSM-IV-R, at least 5 symptoms of depression must be present for a minimum of 2 consecutive weeks. At least one of these symptoms must be a depressed mood or a loss of interest or pleasure (anhedonia) in normally enjoyable activities. Additional diagnostic criteria include a weight loss or gain of more than 5% over the period of a month, change in appetite, insomnia or hypersomnia, psychomotor agitation or slowing, decreased energy (anergia), feelings of worthlessness or inappropriate feelings of guilt, impaired ability to concentrate, and thoughts of death or suicide. By understanding the specific criteria for diagnosing major depressive disorder, a pharmacist may discern signs and symptoms from a ordinary feelings of sadness and stress. Pharmacists should be aware that patients suffering from depression will often present with physical complaints more commonly than for mood symptoms. Using open-ended questions that also address mood symptoms, a pharmacist may be able to help recognize a previously undiagnosed patient.

To ensure an accurate diagnosis of depression, evaluation of possible confounding variables or conditions that mimic the symptoms of idiopathic depression should be completed. Pharmacists can play a specific role through the review of medication histories for contributing factors. Drugs of abuse, especially alcohol, and some prescription drugs can mimic the presentation of depressive symptoms. In addition, many disease states are commonly associated with depression, and clinicians should have a high index of suspicion when patients develop new physical or mood symptoms and they have one of these comorbid disease states. Patients who have had a recent cerebrovascular accident, uncontrolled pain, postmyocardial infarction, or are diagnosed with AIDS tend to have greater risk of developing depression than the general population. Additionally, people with other psychiatric disorders have symptoms similar to depression or have a higher risk of developing comorbid depression than in the general population. One subtype of depression is dysthymia, which differs from major depression primarily due to differences in symptom length and severity. In addition, the clinician must determine if the depressive symptoms are part of schizophrenia, bipolar disorder, schizoaffective disorder, eating disorder or an anxiety disorder or the patient has developed depression secondary to a primary psychiatric condition. Patients with psychiatric disorders complicated by depression require a different pharmacological approach than do patients with unipolar depression alone.

It is important for practitioners to use open-ended questions that focus on extrapolating the core features of the illness. When interviewing a patient and conducting an initial evaluation, the pharmacist should pay special attention to the patient’s appearance, including appropri-
ateness of dress, grooming, and hygiene that may decline with worsening of symptoms. Feelings of hopelessness or helplessness, loss of enjoyment, a lack of energy, and suicidal thoughts are more specific to depression and help distinguish between normal sad mood, medical conditions with physical complaints similar to depression, and true major depression. Suicidal thoughts should be specifically explored thoroughly to assess, if identified, the necessity of immediate referral. If the patient has a plan, and/or the means to accomplish the plan, they are at imminent suicidal risk. In addition, the clinician should note any changes in appetite and sleep patterns, which may also be indicative of a depressed state. Simple observation and basic questioning will alert a pharmacist to symptoms of depression.

PSYCHOMETRIC ASSESSMENT SCALES

The actual diagnosis of major depression can only be made through an extensive interview process and review of past psychiatric histories, critical life events, and family histories. Ordinarily, patients will present with vague physical complaints including insomnia or loss of appetite. These can be important clues in developing a diagnosis but do not make the diagnosis. No single method of diagnosing depression is preferred, although a number of depression rating scales are available to provide a systematic assessment of symptoms and their severity. Traditionally, the primary efficacy measures for antidepressant therapy have been to observe at least a 50% reduction in symptoms as determined by a depression scale. A number of different assessment scales have been developed to aid in the assessment of the severity of symptoms.

The Hamilton Rating Scale for Depression (HAM-D) was first described in 1960 as an effort to upgrade the assessment tools that were available for depression. The scale is used in patients who are recognized to be suffering from depressive disorder and is used mainly to assess severity of illness. The interviewer rated scale was developed to use the information from an interview and translate this information into an objective number to assess the severity of illness and changes in the severity of illness. The scale has a 17-item or 21-item version that uses a 3-point or 5-point range to quantify data. There is no distinction in the variables between frequency and/or severity of a symptom; therefore, the rater should account for both when choosing the appropriate response. For example, the first question to be answered by a clinician using information from an interview is depressed mood (sad, hopeless, worthless) and should be rated (0) absent; (1) these feeling states indicated only on questioning; (2) these feeling states spontaneously reported verbally; (3) communicates feeling states nonverbally—that is, through facial expression, posture, voice, and tendency to weep; and (4) patient reports virtually only these feeling states in his spontaneous verbal and nonverbal communication. The higher the score on the HAM-D, the more severe the depression, with a score greater than 17 being the cut-off for mild to moderate depression.

The reliability of the HAM-D is high, in part due to a strong interrater reliability. In contrast, the validity of the HAM-D has been questioned due to the perceived inability of the HAM-D to assess the severity or type of depression due to the heavy dependence on the presence of physical symptoms. This reduces the overall validity of the scale's ability to assess the global severity of the depression. Some of the particular items of the HAM-D that have been called into question include the questions that measure obsessive symptoms, loss of insight, agitation, and hypochondriasis, as these items are not generally associated with the global assessment of severity. The HAM-D is thought to more accurately assess the behavioral characteristics of depression, rather than measure...
reduced concentration and anhedonia. In addition, the HAM-D has been criticized for not being sensitive enough to assess change in symptom status, which is important when measuring efficacy in clinical trials. Another potential problem is that the HAM-D includes sedation as a measured value. Scoring sedation may introduce bias, as these symptoms could be an adverse effect secondary to medication rather than a true symptom of depression. Despite its criticisms and shortcomings, the HAM-D continues to be the most commonly used efficacy measure in antidepressant clinical trials.

The Montgomery-Asberg Depression Rating Scale (MADRS) was developed to be sensitive to treatment effects between antidepressant medication. The scale was constructed by using items from the Comprehensive Psychopathological Rating Scale to formulate a rating scale that would be useful to clinicians. Ten items were chosen to compose the MADRS. These 10 items included feelings of sadness, changes in sleep, changes in appetite, concentration, lassitude, inner feelings, pessimistic thoughts, and suicidal ideation. These 10 items were assessed on a 7-point scale. One unique property of this scale is that it uses both observational information of the clinician and self-reported information from the patient.

In comparison with the HAM-D, the MADRS has shown favorable sensitivity at detecting the change in severity of depressive symptoms. Overall, the MADRS is believed to be extremely valid when determining efficacy in antidepressant trials and is gaining increasing acceptance among researchers.

The Beck Depression Inventory (BDI) was first published in 1961 and is a commonly used self-rated scale designed to measure the behavioral symptoms of depression. The BDI is composed of 21 categories of symptoms. Within each category are graded, specific, self-behavioral statements that are reflective of cognitive symptoms of depression. The statements are graded 0–3 based on their degree of symptom severity, with 0 being a neutral statement and 3 being a symptom of maximal severity. For example, the ratings for “Sense of Failure” are as follows: (0) “I don’t cry more than usual,” (1) “I cry more now than I used to,” (2) “I cry all of the time now. I can’t stop,” and (3) “I used to be able to cry but now I can’t cry at all even though I want to.” The BDI is administered by a trained interviewer who reads the questions aloud to the person being interviewed and that person is asked to select the statement that they feel most applies to them at that current point in time. In addition to audibly hearing the question, the individual being interviewed was allowed to hold a copy of the scale and to read along. The BDI is sensitive to change, has been validated, and is a very reliable scale when identifying symptoms of major depression.

The Zung Self-Rating Depression Scale is a self-rated scale that was introduced in 1965. The Zung’s goal is to create a self-administered scale that is all-inclusive, detects symptoms, and then quantifies them. This scale is composed of 20 depression-specific questions, 10 written symptomatically positive and 10 written symptomatically negative. Respondents are asked to mark a box that indicates the frequency that they experience a particular feeling defined as a little of the time, some of the time, a good part of the time, or most of the time. Each answer is given a rating of 1, 2, 3, or 4 for a maximum score of 80. An index score for the Zung Depression Rating Scale is calculated by dividing the sum of the scores for the 20 items by the maximum obtainable score of 80. A pretreatment index score of 0.63 to 0.90 is highly suggestive of major depressive disorder. The Zung Self-Rating Depression Scale is a good scale for screening large population subsets; however, its sensitivity to change has been challenged, and it is not routinely used in clinical trials as the primary efficacy assessment tool.
Rating scales are useful to pharmacists in many ways. They can help the pharmacist develop an approach to asking questions even if they don’t use the entire scale. They may, with additional training, use the scales as formalized assessments. Finally, understanding rating scales can help pharmacists evaluate clinical trial data.

CONCLUSION

Pharmacists develop healthy professional relationships with their patients through counseling about medications and disease states. Often the pharmacist becomes a sounding board for patients to voice their frustrations and worries. The pharmacist is likely to be able to detect changes in mood, which may be indicative of depression. In many cases, the pharmacist can employ different interview techniques to provide more depth and insight into the state of the depression. If symptoms are evident, dependent on the setting, assistance should be provided in the form of education or referral for additional assessment, diagnosis, and treatment. The pharmacist may also be responsible for providing an opinion on the selection of an appropriate antidepressant agent and need specific skills in direct patient assessment.

REFERENCES

Defining Response and Attaining Therapeutic Goals for Depression

Naomi A. House and Roger W. Sommi, Jr.

Depression is a cyclic disease with treatment that progresses through an acute, continuation, and maintenance phase, all with different therapeutic goals. Many terms are used to define therapeutic goals and/or treatment response including response, remission, recovery, relapse, and recurrence. For a pharmacist to be effective in working with a patient and their health care team when managing depression, they must have a clear understanding of these terms. A pivotal role for the pharmacist is monitoring a patient’s response to treatment, especially during the acute phase when many stop their therapy. A careful assessment for response is needed 4 to 6 weeks after starting therapy and also 4 weeks after any dosage adjustment or change in antidepressant. Continued assessments for response and/or relapse are needed throughout the continuation phase. By understanding the overall approach to treating depression, along with the specific terms associated with response, the pharmacist can make a meaningful contribution to a patient’s treatment strategy.

KEY WORDS: depression, antidepressant agents, response, remission, recurrence.

INTRODUCTION

MAJOR DEPRESSION IS a common medical condition. In the primary care setting, about 20% of patients have depression.1 About 10% of the population has had an episode of major depression in the past 12 months, whereas 17% have an episode in their lifetime.2 Lifetime prevalence is higher for females at 26% versus 12% for males. The first depressive episode most often occurs in young adults, with a peak during the late 20s. However, people of any age may experience a major depressive episode. Symptoms usually develop gradually over several weeks and last at least 6 months, usually longer, if untreated.3 Treating depression early in the episode prevents further decline of occupational and social functioning. Once an individual is diagnosed with depression, reducing the symptoms significantly becomes the first goal of therapy. The main goal, however, is to achieve complete symptom resolution or allow a patient to become asymptomatic for an extended period of time. The Agency for Health Care Policy and Research, now called the Agency for Healthcare Research and Quality, released a clinical practice guideline in 1993 that summarizes the goals of therapy as to reduce and ultimately to remove all signs and symptoms of the depressive syndrome, to restore occupational and psychosocial function to that of the asymptomatic state, and to reduce the likelihood of relapse and recurrence.4

TERMINOLOGY

In 1991, Frank et al.5 reviewed the major depression literature and discovered that depres-
sion treatment outcome terminology is not consistent across studies. After reviewing the studies, they defined five terms related to depression, sometimes called the five “Rs” of depression: response, remission, recovery, relapse, and recurrence. The term response is defined as the point at which depressive symptoms have improved to the point that they do not meet criteria for major depression. However, the patient may still have symptoms. Response also implies treatment, either with medications or psychotherapy. Often, this is described as a 50% to 75% reduction in symptoms. Most clinical trials for antidepressants define a clinical response as a 50% reduction from baseline in the Hamilton Depression Rating Scale total score. Care must be taken in patients who are severely depressed. A 50% reduction in scores may still represent significant depressive symptoms, that is, significant pathology remains despite the decrement in symptoms. When treatment begins, improvement in symptoms is expected to occur within a few weeks. Adjustment in treatments may need to occur after the initial reduction in symptoms to optimize the response. Response describes a reduction in symptoms, not complete elimination of symptoms. Response once was considered to be an acceptable treatment goal, requiring no further interventions. However, remission has become the new standard.

Full remission is defined as a period of time in which the individual is symptom free and has returned to baseline level of functioning. Ideally, when a person is first diagnosed with depression, a full remission within a few months is the desired treatment goal. Full remission may occur spontaneously after many months or can be achieved sooner with active treatment.

Response is the ultimate goal in managing depression and is the next phase following remission. Recovery is defined as an absence of symptoms for a sustained amount of time, usually 4 to 9 months after acute treatment. During the period of recovery, the key decision of whether or not to discontinue treatment is made. If there are risk factors such as serious suicide attempts, multiple medication trials, or comorbid psychiatric conditions, the patient should continue into a maintenance phase.

Depression is a cyclic disorder. A person can experience periods of depressed mood and periods of euthymia. It is this waxing and waning of symptoms that leads to relapse and recurrence. Often during an episode of depression, a person may get worse, either during remission or recovery. If symptoms return during remission to such a degree that they satisfy the criteria for a major depressive episode, then the patient has relapsed. If a person had achieved remission spontaneously without treatment, a relapse signifies the need to intervene with a treatment. If remission was achieved using active treatment, a relapse signals the need for a change in therapy, such as a dose increase, a change in medication, re-evaluation of contributing factors, and so forth. A relapse is part of an ongoing episode and not a new episode of depression.

A recurrence, in contrast, signifies a new depressive episode. A recurrence occurs only during or after recovery has occurred. About 50% of the population experiences a recurrence over their lifetime. After three episodes, the risk of further recurrences increases to 90%. If recovery is achieved without active treatment, a second episode indicates the need for active treatment because each new recurrence increases the risk of further episodes. After a third depressive episode, treatment should be continued to prevent further recurrences.

PHASES OF TREATMENT

Once an accurate diagnosis of major depressive disorder is made, most clinicians will recommend treatment, especially if symptoms are moderate to severe or functional impairment is
present. Treatment may consist of medication, psychotherapy, or a combination of both. The patient’s wishes should be considered in choosing which of these alternatives are used. To achieve response, remission, and finally recovery, treatment is divided into 3 phases: acute, continuation, and maintenance.

The acute phase occurs once treatment is initiated and continues until full remission occurs up to 8 to 12 weeks in length. Once full remission has been achieved, treatment moves into the continuation phase. Because there is a 40% to 60% risk of relapse if the antidepressant medication is withdrawn after early response, antidepressant therapy must continue for another 4 to 9 months.8 During the continuation phase of treatment, the goal is for the patient to remain in remission. At the end of the continuation phase, medications may be tapered off or continued in the maintenance phase. The final phase, reserved primarily for patients with recurrent illness or significant risk factors, is maintenance, during which the goal is the prevention of recurrent depressive episodes.

TREATMENT

Depression management can include medications or nonpharmacological interventions including cognitive-behavioral therapy or psychotherapy. Because all antidepressants have shown efficacy in placebo-controlled trials, any of the antidepressants available may be used as a first-line agent.9 Tricyclic antidepressants and monoamine oxidase inhibitors have more adverse effect burden, and therefore are reserved as second- or third-line agents. Choice of an antidepressant should be made based on balancing the drug’s adverse effect profile to the individual patient’s needs, potential for drug interactions, and history of response. Once an antidepressant is chosen, it is key that it be used correctly to achieve the goals of response, remission, and recovery. The rule of thumb is to use the “adequate dose for an adequate time.”

Some antidepressants may need to be titrated to a therapeutic dose to minimize the adverse effects. There is a risk for failure if the dose is not increased to the therapeutic range (Table 1). Once the target dose is achieved, an additional 4 to 6 weeks are needed to allow for a response to occur.4 There is some evidence that suggests antidepressants with more than one pharmacological activity, such as venlafaxine and mirtazapine, may have quicker onset of action.10–12 However, a meta-regression analysis of randomized trials comparing selective serotonin reuptake inhibitors to dual action antidepressants was done, and no difference was found between the various antidepressants.13

A critical time point for evaluation of response is after 4 to 6 weeks of treatment at the target dose. If there is no change or no response, then it is appropriate to consider another antidepressant. When a partial response occurs, a dose increase may be necessary.14 After each dosage or medication change, the antidepressant should be continued for a minimum of 4 weeks to fully assess response. In some patients, numerous trials with different antidepressants are needed to achieve a response and remission. Once remission is achieved, the dose that produced the remission should be maintained for another 4 to 9 months throughout the continuation phase.

Baseline patient education focusing on the longitudinal nature of therapy is critical to

Table 1. Antidepressant Medications and Dosage14

<table>
<thead>
<tr>
<th>Type/Class</th>
<th>Medication</th>
<th>Target Dose</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective serotonin reuptake inhibitors (SSRIs)</td>
<td>Fluoxetine</td>
<td>20</td>
<td>40–80</td>
</tr>
<tr>
<td></td>
<td>Paroxetine</td>
<td>20–30</td>
<td>40–60</td>
</tr>
<tr>
<td></td>
<td>Sertraline</td>
<td>50–100</td>
<td>150–200</td>
</tr>
<tr>
<td></td>
<td>Citalopram</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>Tricyclic antidepressants (TCAs)</td>
<td>Amitriptyline</td>
<td>150–200</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>Desipramine</td>
<td>150</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>Imipramine</td>
<td>150</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>Nortriptyline</td>
<td>75–100</td>
<td>200</td>
</tr>
<tr>
<td>Others</td>
<td>Bupropion SR</td>
<td>200–300</td>
<td>400</td>
</tr>
<tr>
<td></td>
<td>Bupropion</td>
<td>225–300</td>
<td>450</td>
</tr>
<tr>
<td></td>
<td>Mirtazapine</td>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Nefazodone</td>
<td>300</td>
<td>600</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine</td>
<td>150–225</td>
<td>375</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine XR</td>
<td>75</td>
<td>225</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors (MAOIs)</td>
<td>Phenelzine</td>
<td>45–60</td>
<td>90–120</td>
</tr>
<tr>
<td></td>
<td>Tranylcypromine</td>
<td>30–40</td>
<td>60–80</td>
</tr>
</tbody>
</table>
avoid early termination of therapy. Early termination can be mistaken for failures, leading to unnecessarily complex medication treatments being given to patients.

Patients may discontinue antidepressant therapy for various reasons. Linden et al. evaluated early termination rates and found that antidepressants were discontinued during the first 10 weeks 31%–48% of the time. When the reason was “good response,” the median of treatment duration was 43 days. When adverse events caused discontinuation, the median treatment duration was 15 days. Educating patients on potential adverse effects and providing strategies to minimize adverse events may also improve compliance and treatment duration. Monitoring for both adverse effects and for response/remission throughout the acute and continuation phases will provide continuity of care and optimize therapy, as some side effects may only become apparent later in treatment.

Monitoring therapy continues to be important. Sexual dysfunction caused by some of the antidepressants, in particular, the selective serotonin reuptake inhibitors, may be more concerning to patients during the continuation phase when depression symptoms have abated. To make this discussion easier, rating scales might be used. One such scale is the Arizona Sexual Experience Scale, a 5-item questionnaire. Since the recurrence rate of antidepressants is about 50% after the first episode, patients who are currently stable may discontinue their medication at the end of the continuation phase. Antidepressants should be tapered slowly, no more than 25% a week, to reduce the risk of withdrawal to minimize the risk of the re-emergence of depression symptoms if tapered too quickly.

Major depressive disorder has become one of the more prominent disease states in primary care. Closely monitoring a patient for response, remission, and recovery and being aware of potential adverse effects will help to maximize drug therapy. Encouraging patients to stay on their medication throughout the acute and continuation phases of therapy will help to prevent relapses. Most important, by reducing and/or removing symptoms completely, antidepressant therapy leads to restoring occupational and social functioning.

REFERENCES


Antidepressants: Using Pharmacology to Individualize Therapy

Daniel J. Dugan

The pharmacotherapy of depression has undergone significant change in the last two decades. A new generation of antidepressant agents has displaced older drugs as first-line therapies for depression. The clinician that seeks optimal outcomes for treatment of depression must be familiar with all of the available antidepressant agents. This article will discuss the pharmacologic profile of antidepressants currently marketed in the United States, identifying similarities and differences that have clinical relevance in the management of depression. Drug selection with an emphasis on antidepressant receptor affinity will be reviewed.

KEY WORDS: antidepressant, receptor affinity, drug selection.

INTRODUCTION

The last three decades have delivered an explosion of pharmacotherapeutic options for the care of persons living with depression. Currently in the United States, more than 20 drugs are marketed as antidepressants or have a pharmacologic profile consistent with antidepressant activity (e.g., fluvoxamine, clomipramine). The clinician that seeks optimal outcomes for the treatment of depression must have an understanding of the differences and similarities among the available agents in the domains of efficacy, safety, and tolerability. This article will review the pharmacologic profile of available antidepressants, identifying similarities and differences that have clinical relevance in the management of depression.

ANTIDEPRESSANT MECHANISMS

All available antidepressants work by directly altering the activity of one or more of the biogenic amine neurotransmitter systems, serotonin, norepinephrine, and dopamine. This alteration leads to changes in neurotransmission that precipitate an antidepressant response. By one theory, antidepressant efficacy is associated with initial increased activity of neurotransmitters (drug effect) and subsequent downregulation of postsynaptic receptors (body’s response).1 Antidepressants can work through a variety of presynaptic and postsynaptic mechanisms to increase activity of one or more of these neurotransmitter systems. Differences in action at these various sites leads to clinically significant differences that may be exploited to optimize patient response or minimize side effects in sensitive populations. Similarly, antidepressants bind receptor systems that are unrelated to their antidepressant activity. Effects associated with activity at these incidental receptor systems can have a significant impact on the tolerability and safety of these agents. To better understand anti-
depressants, it is useful to divide the agents into classes.

Classes of antidepressants may be ordered by chemical structure, historical sequence or by presumed mechanism of action. For example, amitriptyline, imipramine, nortriptyline, and desipramine can be grouped by common chemical structure when we identify these as tricyclic antidepressants. In terms of historical sequence, these may be identified as first-generation antidepressants, because these were among the first drugs used for the treatment of depression. Based on receptor affinity, imipramine and amitriptyline may be identified as mixed norepinephrine and serotonin reuptake inhibitors, while desipramine and nortriptyline could be identified as relatively selective norepinephrine reuptake inhibitors. All of these agents share activity at other receptor systems that are unrelated to their antidepressant action, and which significantly affect tolerability and safety. Therefore, the 4 may again be grouped together on the basis of affinity for muscarinic receptors, histamine receptors, and the sodium pump (Na+/K+/ATPase). Each approach to the classification of these 4 drugs is useful in developing an understanding of them. This review will attempt to group drugs by common pharmacologic mechanisms associated with clinically relevant outcomes. This will provide a means for identifying similarities and differences in drug effects that affect patient care and should inform drug selection.

**MONOAMINE OXIDASE INHIBITION**

The antidepressant quality of the monoamine oxidase inhibitors (MAOIs) was discovered by accident. A precursor to contemporary MAOIs was being investigated as antituberculous agents when treated patients with comorbid depression experienced relief of depressive symptoms.2

Monoamine oxidase (MAO) is a presynaptic catabolic enzyme for dopamine, norepinephrine, and serotonin. The two subtypes of MAO are “A” and “B.” MAO-A is responsible for metabolism of norepinephrine and serotonin, while MAO-B is associated with dopamine metabolism. Tranylcypromine, isocarboxazid, and phenelzine are nonselective and irreversible inhibitors of both subtypes of MAO. Inhibition of MAO enzymes leads to increased availability of the neurotransmitter substrates of these enzymes both centrally where an antidepressant effect is achieved and peripherally where blood pressure control may be altered. Treatment with an MAOI has an associated risk of hypertensive crisis from interactions with food or other drugs. The “cheese” reaction can occur when tyramine-rich foods are ingested. Tyramine, a normal MAO-A substrate, can act as a false neurotransmitter at noradrenergic receptors in the vasculature leading to markedly increased resistance. At therapeutic doses, MAOIs have virtually no affinity for other pharmacologically active sites in the body and so are generally well tolerated. Despite this, the risk of hypertensive crisis and the attendant dietary restrictions limit these drugs to last-line care in most practices.

At present, a reversible selective inhibitor of MAO-A (RIMA) named moclobemide is used in Europe. Because it is a reversible antagonist, the risk of hypertensive crisis with this agent is greatly reduced. Future drug development in the United States may lead to the marketing of a RIMA agent.3,4

**TRICYCLIC AND HETEROCYCLIC ANTIDEPRESSANTS**

The antidepressant effect of tricyclic antidepressants (TCAs) was also discovered by serendipity. The search for an improved antipsychotic yielded some of the earliest antidepressant compounds (imipramine, amitriptyline). While these agents were poor antipsychotics, they were discovered to possess good antidepressant qualities. Subsequent drug development led to the agents that are collectively called the TCAs. These drugs, which were once considered the gold standard treat-
ment for depression, all share tolerability and safety concerns due to their diverse receptor affinities.

TCAs inhibit reuptake of norepinephrine as well as serotonin by blockade of the transport proteins associated with these neurotransmitters. Blockade of the reuptake transporters (also called reuptake pumps) leads to increased synaptic neurotransmitter concentrations and eventual antidepressant effect. With the exception of clomipramine which acts primarily as a serotonin reuptake inhibitor, TCAs have greater affinity for the norepinephrine reuptake transporter (Table 1). Desipramine and nortriptyline are fairly selective norepinephrine reuptake inhibitors, while amitriptyline and imipramine have mixed norepinephrine and serotonin effects. Activity at other receptors in the body is associated with adverse effects at therapeutic doses.

The strongest activity of TCAs is at the histamine H₁ receptor. Imipramine, amitriptyline, maprotiline, trimipramine, and doxepin are all more potent than diphenhydramine as antagonists of histamine H₁ receptors. Because of this affinity, these agents are effective for allergic conditions and as hypnotics. Blockade of histamine receptors in the central nervous system (CNS) is associated with sedation, weight gain, and potentiation of the CNS depressant effects from other drugs. While initial sedative qualities may be a desirable feature for treatment of persons with agitated depression, this effect may significantly decrease the long-term tolerability of these agents. Of the TCAs, desipramine has the lowest risk of antihistamine effects.

TCAs are moderate antagonists of the muscarinic acetylcholine receptors as well as the α₁-adrenergic receptors. Central and peripheral effects associated with anticholinergic activity include memory impairment, increased heart rate (10–20 beats per minute), dry mouth, blurred vision, constipation, and urinary retention. Hypotensive effects associated with peripheral α₁-adrenergic inhibition may cause orthostasis, dizziness, and syncope. Central and peripheral effects on the cholinergic and adrenergic systems are often most profound in the elderly, and dose adjustments should be made for patients older than age 65.

The effect of TCAs on sodium channels in the heart can cause prolongation of the QT interval at therapeutic doses. This effect is similar to the action of type la antiarrhythmic medications such as quinidine. TCAs should be avoided in persons treated with antiarrhythmic medications. High-dose tricyclic therapy may precipitate first degree heart block and may be proarrhythmic in susceptible patients. TCAs are very dangerous in overdose due to accelerated heart rate associated with anticholinergic effects and delayed conduction in the myocardium due to blockade of sodium channels. These combined effects have led to fatal arrhythmias. Seizures seen in overdose may also be related to sodium channel blockade.

<table>
<thead>
<tr>
<th></th>
<th>NE Reuptake</th>
<th>SHT Reuptake</th>
<th>Muscarinic</th>
<th>Alpha1</th>
<th>Histamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>++</td>
<td>+</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Imipramine</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>++++</td>
<td>+/–</td>
<td>+</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Desipramine</td>
<td>++++</td>
<td>+/–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>+</td>
<td>++++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Doxepin</td>
<td>+</td>
<td>+/–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>++++</td>
<td>+/–</td>
<td>+/–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>++++</td>
<td>+/–</td>
<td>+/–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Trimipramine</td>
<td>+</td>
<td>–</td>
<td>+++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Maprotiline</td>
<td>++++</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>++++</td>
</tr>
</tbody>
</table>

TCAs were for many years the standard first-line therapy for treatment of depression. Drug development in the past two decades has yielded new antidepressant agents with equal efficacy to the TCAs but with improved tolerability and decreased risk in overdose. The first of these new agents were the serotonin reuptake inhibitors.

**SELECTIVE SEROTONIN REUPTAKE INHIBITION**

Selective serotonin reuptake inhibitors (SSRIs) are a class of drugs named for their mechanism of action. This nomenclature reflects a shift in drug development. Prior to the SSRIs, drug development proceeded from a trial and error design approach, with new agents being developed from chemical adjustment of predecessor compounds. Nomenclature proceeded from the chemical structure of the compounds, rather than the activity of those compounds. With refinement in techniques and the development of theories of antidepressant mechanisms, new agents were designed to perform discrete actions in the CNS.

Like their tricyclic predecessors, the SSRIs act as reuptake inhibitors. Unlike the TCAs, these drugs have greater affinity for the serotonin reuptake transporter than for any other central or peripheral receptor system. The SSRIs have been very successful and presently are the most commonly prescribed class of drug for the treatment of depression. The SSRIs include paroxetine, sertraline, fluoxetine, citalopram, and fluvoxamine. Despite superior safety in overdose and improved tolerability when compared to older drugs, the SSRIs are not without side effects.

The clinical efficacy as well as the side effects of the SSRIs are mediated by their action at the serotonin system. Clinical consequences associated with serotonin agonism are generally dose dependent and include gastrointestinal problems (nausea, diarrhea), increased anxiety, sexual dysfunction, and sleep disturbance. Gastrointestinal complaints including nausea and diarrhea are associated with initiation of treatment or dose increases. These side effects are generally mild in nature and will be self-limiting with time on treatment. Patients with a comorbid anxiety disorder will frequently experience an exacerbation of anxious symptoms on initiation of SSRI treatment. For these patients, a gradual titration to a desirable antidepressant dose over 1 to 2 weeks can minimize this effect.

Longer term problems associated with SSRIs include sexual dysfunction, sleep disturbance, and modest weight gain. Sexual side effects include loss of interest, erectile dysfunction, and failure to achieve orgasm and may occur in 26% to 70% of patients treated with an SSRI. Because symptoms of depression can include decreased libido, patients frequently misinterpret sexual side effects as a continued symptom of depression or as a failure in their intimate relationship. It is important for clinicians to obtain baseline information about sexual satisfaction and to actively monitor this domain during antidepressant treatment. In patients with diminished sexual interest associated with depression, restoration of the premorbid libido should be expected within 4 to 8 weeks. Continued disinterest or onset of another sign of sexual dysfunction (e.g., anorgasmia) may suggest an SSRI-induced side effect. In this case, a dose reduction is a reasonable option if a lower dose can be expected to support continued antidepressant efficacy. Some patients benefit from a dose holiday on the day planned for sexual intimacy. This strategy must be undertaken with care as withdrawal effects of SSRIs can also occur after one or more missed doses of a short half-life agent such as paroxetine. Other strategies include selection of an antidepressant drug...
Disturbed sleep is a common presenting symptom of depression. While all anti-depressants can affect normal sleep, the SSRIs, with minimal activity at receptor systems that may cause sedation, can have more pronounced effects. This class of antidepressants cause increased sleep latency (delay falling asleep) and decreased REM sleep. A minority of patients experience persistent insomnia, characterized by difficulty falling asleep, frequent awakenings, or nonrestful sleep. It has also been shown that patients with a sleep disorder associated with depression often experience improvement in their sleep with SSRI treatment. One common side effect of early SSRI treatment is increased vivid dreams. Patients are often reassured to learn that such dreams can be a benign side effect of SSRI treatment.

The generation of drugs brought to market in the last two decades reflect continued refinement of molecular biology and the development of novel approaches to mechanisms designed to elicit an antidepressant response or minimize side effects. Among the drug classes reviewed thus far, multiple agents have shared similar mechanisms. With newer agents, each drug entity presents novel and unique pharmacology that reflects an innovation in antidepressant therapeutics.

VENLAFAXINE

Venlafaxine is unique among antidepressants currently marketed in the United States. The mechanism of action for this drug is similar to the TCAs. Venlafaxine acts through inhibition of both serotonin and norepinephrine reuptake but has very low affinity for other neurotransmitter systems. Venlafaxine’s affinity for these two reuptake transport proteins is not equal. At lower therapeutic doses, venlafaxine mostly binds the serotonin reuptake pump, while at higher doses, inhibition of norepinephrine becomes more coequal.

Side effects of this drug are similar to those seen with serotonin reuptake inhibitors. At low therapeutic doses, serotonergic side effects predominate (nausea, sexual dysfunction, and insomnia). With higher doses, these side effects can become more marked, and the onset of noradrenergic side effects can be seen. These include increased blood pressure, tremor, and diaphoresis. Blood pressure should be monitored regularly, especially in those with medication-controlled hypertension or borderline high blood pressure. For most patients, changes are usually limited to systolic increases of 5–10 mm of mercury, but greater effects are possible. Side effects associated with venlafaxine treatment can be greatly minimized by use of the extended release formulation.

SEROTONIN 5-HT2A RECEPTOR ANTAGONIST

The neurotransmitter serotonin binds to more than 15 different subtypes of receptors. Presynaptic inhibition of serotonin reuptake or catabolism can lead to an increase in the postsynaptic serotonin signal. The postsynaptic serotonin2A (5-hydroxytryptamine; [5HT2A]) receptors are another target for antidepressant action that can lead to an increased postsynaptic signal. These receptors are opposed to the postsynaptic 5HT1A receptor in a “gas-pedal/brake” relationship. Activation of the 5HT1A receptor is normally balanced by activation of the 5HT2A receptor. Inhibition of the 5HT2A receptor leads to disinhibition of the 5HT1A receptor and increased serotonin signal to the postsynaptic neuron.

Trazodone and nefazodone have similar chemical structures and share a high affinity for the 5HT2A receptor as well as a modest affinity for the serotonin reuptake transporter protein. Trazodone is also an antagonist at α1-adrenergic receptors. Activity on this system may account for the significant sedation and orthostatic seen with this drug at therapeutic doses. These side effects limit the use of this drug as an
Antidepressant but have led to its exploitation as a non–habit-forming sedative-hypnotic. Nefazodone does not share activity at the 1 adrenergic receptor and is largely free of orthostatic effects. The effect of nefazodone on sleep is unique among antidepressants.

Antidepressants tend to alter polysomnographic measures of sleep (e.g., sleep EEG). Decreased REM sleep and disrupted slow wave or deep sleep is a finding common to most studies of the impact of antidepressants on sleep. These laboratory findings are associated with decreased sleep quality and, in some subjects, a complaint of not feeling rested on awakening. As noted above, drugs with significant antihistaminergic activity tend to decrease sleep latency (time to fall asleep) but may also be associated with daytime somnolence. Nefazodone has been shown to both decrease sleep latency and increase REM sleep. For patients with a comorbid, chronic sleep complaint, nefazodone may diminish antidepressant-associated sleep problems.

Antagonism of the 5HT2A receptor gives nefazodone an advantageous side effect profile when compared to SSRIs. As stated above, unopposed serotonin activation is associated with increased anxiety, insomnia, and sexual dysfunction. As these side effects are greatly reduced in nefazodone-treated patients, we can deduce that these side effects are at least in part mediated by 5HT2A receptors. Side effects of nefazodone treatment have a low incidence and include dry mouth, dizziness, and daytime somnolence.

BUPROPION

Bupropion is a unique antidepressant at both chemical and pharmacologic levels. It is a weak inhibitor of dopamine and norepinephrine reuptake and has a single-ring structure rather than the typical fused rings of other antidepressant molecules. Its in vitro activity at norepinephrine and dopamine reuptake sites suggests weaker antidepressant properties than are actually seen in patients. This mismatch between in vitro activity and clinical experience may be explained by the presence of active metabolites. Bupropion undergoes extensive first-pass hepatic metabolism. Its antidepressant qualities may be due to the hydroxy-bupropion metabolite that is more active in vitro than the parent compound at both dopamine and norepinephrine reuptake inhibition. This metabolite predominates in cerebrospinal fluid after administration.

The side effect profile of bupropion can be predicted from dopaminergic activity. Bupropion tends to be activating and may cause tremor, insomnia, restlessness, and loss of appetite. Stimulant effects may be desirable in depressed patients experiencing psychomotor retardation, hypersomnia, or hyperphagia. On the other hand, most clinicians would prefer to avoid these effects in patients that have experienced significant weight loss with depression or who have an agitated presentation. Bupropion is associated with a dose-related lowering of the seizure threshold. This rarely leads to seizures in patients treated at therapeutic doses but has led to serious health risks in overdose. Bupropion is less lethal in overdose than TCAs, but seizures following overdose ingestions have led to death in a few cases reported.

MIRTAZAPINE

The α2-adrenergic receptor is both a presynaptic autoreceptor and a neuromodulatory postsynaptic heteroreceptor. Located on the adrenergic nerve terminal, (i.e., proximal to the nerve synapse), the autoreceptors control norepinephrine release. The α2 autoreceptor is activated when neurotransmitter is released into the synapse and causes inhibition of con-
continued release. At neuron cell bodies (i.e., distal from nerve terminals), α₂ heteroreceptors modulate cell function of serotonin neurons. Inhibition of α₂-adrenergic receptors by mirtazapine leads to increased noradrenergic and serotonergic transmission. Inhibition at the nerve terminal causes increased firing of norepinephrine neurons, while activity on cell bodies augments norepinephrine and serotonin release throughout the brain. In addition, mirtazapine is an inhibitor of 5HT₂ receptors, which leads to selective increased transmission through serotonin 5HT₁A. This mechanism, as observed with nefazodone, tends to diminish side effects that might otherwise be expected with unmodulated serotonin.²,¹⁰

An increase in transmission through norepinephrine and serotonin systems is the mechanism associated with an antidepressant effect. Mirtazapine also binds histamine H₁ receptors. Like the TCAs, side effects with mirtazapine associated with antihistamine effects include drowsiness and daytime sedation, as well as appetite stimulation and weight gain. For some patients, these effects may be transient or offset by increased adrenergic stimulation as doses are adjusted upward.

**DRUG SELECTION**

Despite the diversity in pharmacologic mechanisms with which various antidepressants elicit an antidepressant response, all antidepressants have shown approximately equal efficacy for eliciting an antidepressant response. About 2 of every 3 patients treated with a given agent will experience a remission of the depression. Except in the case of a patient with a history of prior response, product selection on the basis of perceived differences in efficacy for the treatment of depression (i.e., faster onset, greater numbers of responders, greater magnitude of response) are unfounded.¹¹ Frequently, clinicians seek a given agent or class of agents for a subpopulation of depressed persons because there is a perception that response to the selected therapy will be superior to other possible treatments. Scientific investigation to assess the value of clinical experience in predicting response with a given agent or class of agents is limited.

A more rational approach to the selection of an antidepressant therapy may be based on an assessment of expected safety and tolerability of available agents for each patient. Safety considerations with newer agents is most often a concern with the potential for drug metabolitic drug interactions. This topic is reviewed elsewhere.¹²

Treatment of depression typically should last 9 to 12 months for a first episode or longer for a recurrent episode. Minimizing side effects during this sustained treatment may reduce the rate of premature antidepressant discontinuation and the attendant risk of relapse. Side effects that often lead to premature drug discontinuation include sexual dysfunction, weight gain, sleep changes, or daytime drowsiness. A review of the interface of antidepressants and these domains is presented in Table 2. In selecting an antidepressant for a patient with a low threshold for adverse sexual side effects, consider using an agent with serotonin 5HT₂ antagonist properties (nefazodone, mirtazapine) or one that has minimal impact on the serotonin system (bupropion). Agents to avoid would include SSRIs, venlafaxine, and TCAs.

Appetite stimulation and weight gain can be a desired effect with antidepressant treatment. In patients with comorbid obesity, hypertension, diabetes, or osteoarthritis, appetite stimulation and attendant weight gain should be avoided. Agents with high affinity for the histamine H₁ receptor (TCAs, mirtazapine) tend to increase appetite and lead to modest weight gain in a majority of patients. Other antidepressants have shown approximately equal efficacy.
sants can also cause weight gain through as yet poorly understood mechanisms. Bupropion is unique among the antidepressants for causing mildly diminished appetite and weight loss. This is probably mediated by stimulant effects on the dopamine system.

Sleep disturbance is a frequent presenting symptom of depression. Unless it was a preexisting condition, sleep symptoms should normalize with antidepressant therapy. Therefore, the selection of an antidepressant based on acute insomnia or hypersomnia associated with depression is unwarranted. A patient exposed to a sedating antidepressant (TCA, mirtazapine) for a full course of treatment may experience unnecessary daytime drowsiness even when depression has lifted. A short course of a hypnotic agent may better relieve the symptom of insomnia while a less sedating antidepressant takes effect.13 Patients with chronic insomnia and comorbid depression may benefit from treatment with an antidepressant that may be expected to increase overall sleep efficiency (mirtazapine, nefazodone).

**CONCLUSION**

Less than two decades ago, antidepressant therapy entailed treatment with agents that were often poorly tolerated and sometimes of dubious safety. Today in the United States, the SSRIs are the most commonly prescribed class of antidepressant. The improved tolerability and safety of these agents have made them first-line antidepressant choices for many clinicians. Still newer agents have been brought to market in the past decade. These agents have shown modest differences in tolerability over the SSRIs but have not precipitated the tidal shifts in the pharmacotherapy of depression that SSRIs brought about. Clinicians familiar with both newer and older therapies for the treatment of depression will be strengthened in their goal of optimizing outcomes for the patients they serve.

**REFERENCES**


Antidepressant Drug Interactions

Sheila R. Botts and Cara Alfaro

Second-generation antidepressants are more selective in their pharmacological mechanisms and offer fewer side effects and a safer toxicological profile than cyclic antidepressants and monoamine oxidase inhibitors. While the risk for pharmacodynamic interactions is more limited than with older agents with broader receptor effects, the risks for pharmacokinetic interactions is greater. The capacity of selective serotonin reuptake inhibitors to inhibit the metabolic activity of cytochrome P450 isozyme system has spurred over a decade of intense psychopharmacological and pharmacogenetics research to better the understanding of the significance of these interactions. Clinicians have had to increase their knowledge and understanding of drug interaction potential to better manage patients receiving these newer antidepressants. The following is a review of both pharmacodynamic and pharmacokinetic drug-drug interactions with antidepressants.

KEY WORDS: drug interactions, cytochrome P-450 system, TCAs, SSRIs.

INTRODUCTION

SECOND-GENERATION ANTIDEPRESSANTS are more selective in their pharmacological mechanisms and offer fewer side effects and a safer toxicological profile than cyclic antidepressants and monoamine oxidase inhibitors. While the risk for pharmacodynamic interactions is more limited than with older agents with broader receptor effects, the risks for pharmacokinetic interactions is greater. The capacity of selective serotonin reuptake inhibitors (SSRIs) to inhibit the metabolic activity of cytochrome P450 (CYP) isozyme system has spurred over a decade of intense psychopharmacological and pharmacogenetics research. Clinicians have had to increase their knowledge and understanding of drug interaction potential to better manage patients receiving these newer antidepressants. Most antidepressants are susceptible to drug interactions, however, not all interactions are clinically significant. Drugs that have a narrow therapeutic index (e.g., tricyclic antidepressants, lithium, etc.) are more likely to be significantly affected by other drugs, resulting in either increased toxicity or diminished efficacy. The following is a review of both pharmacodynamic and pharmacokinetic drug-drug interactions with antidepressants.

REVIEW OF CYP450 METABOLISM

Most drugs undergo biotransformation via phase I (oxidation) and phase II (conjugation) metabolic reactions in the liver. Phase I reactions, such as dealkylation, deamination, and hydroxylation, involve the cytochrome P450 monooxygenases, a group of heme-containing enzymes, located in the endoplasmic reticulum of hepatocytes. CYP450 enzymes are also pres-
ent in the enterocytes of the small intestine, kidneys, lungs, and brain. Conjugation reactions, such as glucuronidation and sulfation, involve the cytosolic enzymes glucuronosyltransferases and sulfotransferases, respectively.

Research in the area of CYP450 has grown exponentially in the past decade. Advances in the application of scientific methods to identify the amino acid sequences of specific CYP isozymes have furthered research in this area. In addition, the ability to fully characterize the CYP metabolism of drugs and their interaction with CYP isozymes has led to clinicians’ being able to predict and prevent clinically significant drug interactions. Although drug interactions involving phase II enzymes can occur, much less research has been completed in this area. Although beyond the scope of this review, an active area of research investigating the role of drug transporters such as p-glycoprotein and organic anion-transporting polypeptide is becoming increasingly important with respect to drug interactions. The focus of this review of metabolic drug interactions will be on the CYP450 enzyme system, largely because this has been the most studied with regard to how antidepressants are metabolized and how antidepressants interact (i.e., inhibit) with various isozymes.

CYP450 isozymes are grouped . . . based on similarity in amino acid sequence.

CYP450 isozymes are grouped into families and subfamilies based on the similarity in amino acid sequence. An Arabic numeral following the prefix CYP indicates the family. Enzyme members of a given family are greater than 40% identical in amino acid sequence (e.g., CYP2). Following the Arabic numeral is a capital letter designating the subfamily of the enzyme. Members of a subfamily are greater than 55% identical in amino acid sequence (e.g., CYP2D). The last digit designates the individual isozyme (e.g., CYP2D6). Thus far, 14 families of cytochrome enzymes common to all mammals have been identified; however, only three of these families (CYP1, CYP2, and CYP3) are currently thought to be important in the metabolism of drugs. The isozymes most relevant in the metabolism of drugs include CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. CYP3A4 is the most abundant isozyme, comprising 25% of the total hepatic CYP, and coupled with its expression in gut wall may be responsible for the metabolism of the majority of xenobiotics.

Polymorphisms have been well described and characterized for at least two isozymes, CYP2D6 and CYP2C19. Due to genetic mutations, some individuals do not possess a functionally active isozyme. These individuals are referred to as poor metabolizers (PMs) due to their inability to efficiently metabolize drugs requiring those isozymes for biotransformation. Extensive metabolizers are those individuals who possess a functionally active isozyme, although the isozyme activity is quite variable from person to person. In addition, ultrarapid metabolizers have been well characterized for the CYP2D6 isozyme; these individuals have extremely high isozyme activity due to multiple gene copies. The percentage of expected PMs in a population varies by ethnic group. PMs comprise 5%–10% of Caucasians and 1%–2% of African Americans and Asians. The clinical importance of polymorphisms is 2-fold. For antidepressants that rely on CYP2D6 for biotransformation, such as desipramine and venlafaxine, PMs will achieve higher concentrations and may experience more adverse effects at usual clinical doses. In addition, antidepressant drugs that inhibit CYP2D6, such as paroxetine and fluoxetine, would have little effect in these PMs because they already possess a functionally inactive isozyme. However, for the vast majority of individuals, administration of drugs that inhibit these isozymes (both those that are polymorphically expressed and those that are not) can have dramatic effects on the concentrations of medications that require these isozymes for biotransformation.
In simplistic terms, a drug that is a substrate for an isozyme may be considered an inhibitor of that isozyme, although the potency of the inhibition will depend on many factors. However, the converse is not necessarily true. Quinidine, for example, is the most potent inhibitor thus far identified for CYP2D6, but it is metabolized by CYP3A4. Table 1 lists some drugs that have been identified as substrates of specific isozymes. Some substrates rely primarily on one specific isozyme for biotransformation. These substrates have been used as “drug probes” in in vivo and in vitro systems. For example, a drug that significantly increases the ratio of desipramine to its hydroxylated metabolite or dextromethorphan to its demethylated metabolite would indicate CYP2D6 inhibition. Examples of other drugs that have been used as probes for specific isozymes include caffeine (CYP1A2); midazolam, alprazolam, erythromycin (CYP3A4); bupropion (CYP2B6); tolbutamide (CYP2C9); and omeprazole (CYP2C19). However, most drugs are metabolized by more than one isozyme. Although tables that list substrates, inhibitors, and inducers are valuable as a basic guide to predict CYP drug-drug interactions, these tables are largely out of date at the time of publication. New information is generated at a rapid pace, and specific variables are not included that would assist in interpreting the clinical significance of interactions, that is, potency of inhibition.

In the recent past, drug interactions were largely identified through postmarketing surveillance programs. However, with the serious adverse sequelae of the terfenadine-ketoconazole interaction, a new sense of awareness and urgency has developed. Scientific advancements in identifying specific CYP isozymes involved in the biotransformation of drugs and the effect of drugs on various isozymes and the ability to predict many drug interactions a priori can now be accomplished. The Food and Drug Administration (FDA) requires that a drug’s CYP metabolism and inhibition profile be determined prior to approval, and many drug companies characterize these early in development when making decisions about whether to pursue drug approval. Although in vitro data are available for most antidepressants, there are a number of limitations.

### Table 1: Select Substrates of CYP isozymes

<table>
<thead>
<tr>
<th>CYP1A2</th>
<th>CYP2C9</th>
<th>CYP2D6</th>
<th>CYP3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline*</td>
<td>Celecoxib</td>
<td>Amitriptyline</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Diclofenac</td>
<td>Clomipramine</td>
<td>Alprazolam</td>
</tr>
<tr>
<td>Clomipramine*</td>
<td>Ibuprofen</td>
<td>Codeine</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Mefenamic Acid</td>
<td>Desipramine</td>
<td>Clomipramine</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Naproxen</td>
<td>Dextromethorphan</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Phenytoin</td>
<td>Donepezil</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Imipramine*</td>
<td>Piroxicam</td>
<td>Flecanide</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Tolbutamide</td>
<td>Fluoxetine</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>Propranolol</td>
<td>S-warfarin</td>
<td>Haloperidol</td>
<td>Imipramine</td>
</tr>
<tr>
<td>Tacrine</td>
<td></td>
<td>Imipramine</td>
<td>Lidocaine</td>
</tr>
<tr>
<td>Theophylline</td>
<td>CYP2C19</td>
<td>Maprotiline</td>
<td>Midazolam</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metoprolol</td>
<td>Mefazodone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nortriptyline</td>
<td>Quetiapine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paroxetine</td>
<td>Quinidine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perphenazine</td>
<td>Sertraline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Propafenone</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Propranolol</td>
<td>Triazolam</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risperidone</td>
<td>Verapamil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thoridazine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trazodone</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Venlafaxine</td>
<td></td>
</tr>
</tbody>
</table>

*CYP = cytochrome P450. *Demethylation of TCAs. Adapted from References [10,63,64,67].

JOURNAL OF PHARMACY PRACTICE, Volume 14, Number 6, December 2001
Many in vivo drug interaction studies have also been performed for this class of psychotropics to better characterize CYP inhibition characteristics. The clinical relevance of these drug interactions will depend on many factors including the toxicity of the affected substrate as well as the availability of alternate metabolic pathways for substrate elimination. In addition, the potency of inhibition of a drug, the dose and concentration achieved, and the number of isozymes inhibited should also be considered when determining the clinical significance of drug interactions.

PHARMACOKINETIC DRUG INTERACTIONS

Tricyclic Antidepressants

Tertiary tricyclic antidepressants (TCAs) are metabolized by multiple CYP isozymes including 1A2, 2C19, and 3A4 (see Figure 1). Hydroxylation of secondary TCAs is primarily mediated by 2D6. Drugs that inhibit or induce these isozymes may affect plasma concentrations of TCAs and alter their efficacy or risk for toxicity. TCAs have a narrow therapeutic index, and thus, most interactions will be clinically important. Paroxetine and fluoxetine, both potent 2D6 inhibitors, have been reported to increase desipramine concentrations up to fourfold. Sertraline coadministration resulted in more modest increases of 30%–100%. Fluvoxamine, a potent 2C, 1A2, and 3A4 inhibitor, has been reported to significantly decrease clearance of imipramine but has minimal effect on desipramine clearance. Although not common clinical practice, SSRIs are sometimes used in combination with TCAs for patients with refractory depression. Other CYP450 inhibitors that have been reported to increase TCA plasma concentrations include bupropion, cimetidine, haloperidol, methylphenidate, oral contraceptives, valproic acid, and venlafaxine. When TCAs are used concomitantly with any one of these agents, it is important to monitor TCA plasma concentrations closely to avoid potential toxicity. Elevated TCA concentrations may result in increased anticholinergic side effects, sedation, and cardiac effects. TCA plasma concentrations >450 ng/ml are associated with arrhythmias, heart block, and sudden death.

Carbamazepine, barbiturates, phenytoin, chloral hydrate, and smoking may increase TCA clearance and result in lower plasma concentrations. Likewise, TCAs have been reported to increase plasma concentrations of carbamazepine, presumably by competing for CYP isozymes. These interactions have the greatest significance when an inducing or inhibiting agent is added or discontinued from a regimen including TCAs. In these instances, a dosage change may be necessary. Clinicians should use plasma concentrations, where applicable, along with clinical signs and symptoms, to guide dosing adjustments. It is important to note that the effect of drug interactions on active metabolites and the resultant potential for toxicity should be considered.

SSRIs

The SSRIs are extensively metabolized by the CYP450 isozyme system. Although these agents possess similar efficacy, their metabolic profiles as well as their capacity for CYP isozyme inhibition vary. Fluoxetine and
sertraline both undergo demethylation to form the active metabolites, norfluoxetine and desmethylsertraline. Norfluoxetine has similar reuptake inhibition as fluoxetine, and both metabolites have similar CYP inhibitory effects as the parent compound.\(^5\) Citalopram is also demethylated to a less active metabolite monodesmethylcitalopram, which is then demethylated to didesmethylcitalopram.\(^5\) Paroxetine and fluvoxamine do not have clinically important metabolites.\(^5\) CYP inducers or inhibitors may alter SSRI pharmacokinetics, but the clinical consequences of these interactions are unclear. Moreover, the wide therapeutic index of SSRIs lessens the likelihood of clinically important interactions. These agents are more likely to result in significant changes in the metabolism of other drugs. The relative inhibitory potential of each SSRI is characterized in Table 2. The evidence for clinically significant interactions with each SSRI antidepressant is discussed below.

### Citalopram

Citalopram and its metabolites, monodesmethylcitalopram and didesmethylcitalopram, are weak inhibitors of CYP1A2, 2C, 2D6, and 3A4. Coadministration of citalopram 40 mg/day with single-dose metoprolol increased the plasma concentration of the beta-blocker by 2-fold. Coadministration of citalopram 40 mg/day with single-dose imipramine did not alter the plasma concentration of the parent TCA but increased the concentration of the secondary amine metabolite, desipramine, by 50%.\(^{11}\) Escitalopram, the active S-enantiomer of citalopram, is currently being studied in depression. Since enantiomers can differ with respect to their CYP inhibition effects (S-fluoxetine inhibits CYP2D6 > R-fluoxetine),\(^{12}\) studies evaluating CYP inhibition effects of escitalopram should be performed.

### Fluoxetine

Fluoxetine, and its major active metabolite norfluoxetine, are potent inhibitors of CYP2D6, as has been evidenced by their effects on desipramine clearance and the CYP2D6 probe, dextromethorphan.\(^{6,13}\) Due to the long half-life of norfluoxetine, 5 to 7 days,\(^5\) significantly elevated desipramine concentrations for approximately 3 weeks following discontinuation of fluoxetine were reported. This suggests that clinicians should consider recently discontinued agents when evaluating for drug interaction potential. Significant interactions may be observed when fluoxetine is coadministered with other CYP2D6 substrates as well (see Table 1). Fluoxetine is a modest inhibitor of CYP3A4 and CYP2C9. Fluoxetine has significantly altered the clearance of 3A4 substrates alprazolam, calcium channel blockers, and carbamazepine.\(^{14–16}\) Coadministration with alprazolam resulted in modest decrease in clearance (27%) but showed a clinical change in psychomotor performance.\(^{14}\) A 50% decrease in the starting dose of alprazolam is recommended when adding alprazolam to fluoxetine. In another study, fluoxetine failed to alter clearance of triazolam (single dose 0.25 mg).\(^{17}\) Despite conflicting data with other triazolobenzodiazepines, caution should be used when combining fluoxetine with clonazepam or triazolam. Significant interactions with the 2C9 substrates phenytoin and warfarin have also been reported.\(^{18}\) Increased monitoring is recommended with each of these agents when coadministered with fluoxetine.

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>1A2</th>
<th>2C9</th>
<th>2C19</th>
<th>2D6</th>
<th>3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>+</td>
<td>++</td>
<td>+/+</td>
<td>+/+</td>
<td>++</td>
</tr>
<tr>
<td>Sertraline</td>
<td>+</td>
<td>+</td>
<td>+/++</td>
<td>+/+</td>
<td>+</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>+/++</td>
<td>+</td>
<td>+/++</td>
<td>+/+</td>
<td>+</td>
</tr>
<tr>
<td>Citalopram</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/–</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/–</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
</tbody>
</table>

+= minimal inhibition, ++ = moderate inhibition, +++ = strong inhibition. Adapted from References \([5,63,64]\).
Fluvoxamine

Fluvoxamine is a potent CYP1A2 and 2C19 inhibitor with modest effects at 3A4 and 2C9. Fluvoxamine has minimal inhibitory effects at 2D6 as evidenced by its failure to alter desipramine kinetics or the CYP2D6 probe, dextromethorphan. When coadministered with imipramine, fluvoxamine resulted in elevated imipramine concentrations owing to its inhibitory effects at CYP1A2, 2C19, and 3A4 (See Figure 1). Significant interactions with 3A4 substrates carbamazepine, calcium channel blockers, triazolobenzodiazepines, cisapride, and nonsedating antihistamines have been reported. The FDA has removed the nonsedating antihistamines, terfenadine and astemizole, and the gastrointestinal motility drug, cisapride, from the U.S. market due to the increased risk of cardiac arrhythmias when coadministered with CYP3A4 inhibitors. Fluvoxamine may decrease the clearance of several drugs metabolized by CYP1A2 (see Table 1). Brozen has reported an increase in the half-life of caffeine from 5 to 20 hours when administered with fluvoxamine. The adverse effects from caffeine may mimic those expected early in SSRI therapy (e.g., anxiety, agitation, insomnia). Dramatic increases in clozapine and theophylline concentrations have been reported when given with fluvoxamine. The adverse effects from caffeine may mimic those expected early in SSRI therapy (e.g., anxiety, agitation, insomnia). Dramatic increases in clozapine and theophylline concentrations have been reported when given with fluvoxamine. The theophylline dose should be reduced by one-third when adding fluvoxamine, and increased monitoring is suggested with clozapine. Interestingly, addition of fluvoxamine 50 mg/day has been used as a clozapine dose-sparing strategy. Fluvoxamine increases warfarin concentrations by 98% with associated increases in prothrombin time. In addition, fluvoxamine has been reported to significantly elevate concentrations of 2C19 substrates propranolol and diazepam.

Sertraline

Sertraline is a modest inhibitor of CYP2D6 with evidence of more significant interactions occurring at higher doses. Sertraline 50 mg/day resulted in an approximate 30% elevation of desipramine concentrations whereas higher daily doses (50–150mg/day) increased desipramine concentrations by 50%–100%. Sertraline has weak inhibitory effects at CYP1A2, 2C, and 3A4. Sertraline has produced small or undetectable interactions with 3A4 substrates alprazolam, clonazepam, carbamazepine, and diazepam. Sertraline has decreased tolbutamide (also a probe drug for CYP2C9) clearance modestly, but the clinical significance is not understood.

Miscellaneous Antidepressants

Venlafaxine

Venlafaxine is demethylated to the major metabolite O-desmethylvenlafaxine (ODV) via CYP2D6 and a minor metabolite N-desmethylvenlafaxine via CYP3A4. A study in poor and extensive metabolizers of CYP2D6 found total drug (Venlafaxine + ODV) to be similar for both groups, suggesting that no dosage adjustment is required when venlafaxine is coadministered with 2D6 inhibitor drugs. However, another group reported adverse events (e.g., palpitations), which may be more pronounced in CYP2D6 PMs, suggesting that some individuals may be more susceptible to adverse events associated with higher concentrations of venlafaxine.

Paroxetine

Paroxetine is a potent inhibitor of CYP2D6 but has minimal activity at other isozymes. Paroxetine may significantly increase the clearance of CYP2D6 substrates such as secondary TCAs (see TCAs), antipsychotics (e.g., thioridazine, risperidone), codeine, and antiarrhythmics (see Table 1). There have also been reports of bleeding diathesis when paroxetine was coadministered with warfarin, but elevations in warfarin concentrations and alterations in prothrombin time were not observed.
single-dose imipramine $C_{\text{max}}$ and $AUC$ by 28% and the $C_{\text{max}}$ and $AUC$ of its metabolite, desipramine, by 40%. 37

Nefazodone

Nefazodone, an antidepressant structurally related to trazodone, is metabolized via CYP3A4 to three active metabolites: hydroxynefazodone, triazoledione, and metachlorophenylpiperazine (m-CPP). 5 m-CPP is metabolized by CYP2D6, and is generally present in small concentrations. 5 However, m-CPP concentrations are reportedly higher in 2D6 poor metabolizers than extensive metabolizers. 38 m-CPP, when administered in studies, has been associated with increased anxiety symptoms. 39 Coadministration of nefazodone with drugs possessing potent CYP2D6 inhibitory properties, such as ritonavir or fluoxetine, can increase m-CPP concentrations and potentially cause anxiety symptoms. 39

Nefazodone is a potent 3A4 inhibitor but has negligible activity at CYP1A2, 2C, and 2D6. Coadministration of nefazodone with 3A4 substrate pimozide is contraindicated due to the increased risk of cardiac arrhythmias. Significant interactions have been reported with buspirone, carbamazepine, triazolobenzodiazepines, cyclosporine, and HMG-CoA reductase inhibitors. 38,42–47 Nefazodone causes substantially elevated plasma concentrations of triazolam and alprazolam. A 75% reduction in triazolam dose is recommended when used with nefazodone. 38 CYP3A4 inhibitors increase the risk of rhabdomyolysis and myositis with HMG-CoA reductase inhibitors, and two such cases have been reported with nefazodone. 45,46

Bupropion

Bupropion is metabolized by CYP2B6 to four major metabolites: erythro-, threo-amino alcohols, and hydroxybupropion. 48 Hydroxybupropion is thought to be the major metabolite, and its $AUC$ is approximately 15 times that of bupropion. Drugs known to affect CYP2B6 (e.g., orphenadrine, cyclophosphamide) would alter the kinetics of bupropion. In vitro data suggest that some SSRIs have the potential to inhibit hydroxylation of bupropion. 49 Carbamazepine has been reported to decrease bupropion plasma levels, suggesting that it induces 2B6. 50 In vitro data also suggest that the protease inhibitors ritonavir, efavirenz, and nelfinavir inhibit CYP2B6 and, therefore, may increase the risk for toxicity, particularly seizures. 51,52 Bupropion does appear to possess some CYP2D6 inhibitory properties. Bupropion 150 mg twice daily increased the $C_{\text{max}}$ and $t_{1/2}$ of single-dose desipramine by 2-fold. 48 Additionally, one case report noted that bupropion increased imipramine and desipramine plasma concentrations with a greater effect on desipramine. 53

Mirtazapine

Mirtazapine is metabolized by CYP1A2 and 2D6 to an 8-hydroxy metabolite and by 3A4 to an $N$-desmethyl and $N$-oxide metabolite. 54 Hepatic enzyme inducers or inhibitors would be expected to alter the metabolism of mirtazapine, but the clinical significance is currently unknown. Both alcohol and diazepam increase the central nervous system (CNS) depressant affects of mirtazapine without significantly altering its metabolism. Based on in vitro data, mirtazapine is considered a weak inhibitor of CYP1A2, 2D6, and 3A4 isozymes.

Reboxetine

Although not currently marketed in the United States, reboxetine may soon be approved for the treatment of depression. Reboxetine is primarily metabolized by CYP3A4 and appears, based on in vitro data, to lack significant effects on CYP1A2, 2C9, 2D6, 2E1, or 3A4. 55 Reboxetine did not significantly inhibit CYP2D6 using the isozyme probe, dextromethorphan, in healthy volunteers. 56

St. John’s Wort

St. John’s wort (SJW), Hypericum perforatum, is an over-the-counter herbal preparation that
may be effective for the treatment of mild to moderate depression. Because the FDA does not regulate these products, manufacturers are not required to show that their preparations are effective (although there are some labeling limitations) or to investigate the potential for drug interaction effects. Several European reports that described breakthrough bleeding with SJW and oral contraceptives and decreasing INR when SJW was added to warfarin therapy, suggested that SJW may possess CYP induction properties. Since then, a number of studies using either CYP probe drugs or clinical drugs have found potent CYP3A4 induction properties of SJW. A pharmacokinetic study evaluating the effects of SJW, 300 mg 3 times daily, with the CYP3A4 substrate, indinavir, found that SJW reduced the AUC of indinavir by 57%. Case reports of transplant rejection secondary to presumed SJW induction of cyclosporine concentrations have also been published. SJW may also induce CYP1A2, although this finding needs to be replicated. Currently, it is unknown which of the components present in SJW is responsible for the CYP induction, although some speculate it may be hyperforin. It should also be noted that the extent of induction effects may be difficult to predict, because there is considerable variability within and between different brand products. Clinicians should be assessing herbal use in patients and counseling with regard to potential interactions with SJW.

**PHARMACODYNAMIC DRUG INTERACTIONS**

TCAs have additive effects with other drugs with similar pharmacological receptor effects (e.g., antimuscarinic, antihistaminic, and alpha-1 antagonism). TCAs may increase the CNS depressant effects of sedative-hypnotics and alcohol. The hypotensive effects of certain sympatholytic antihypertensive agents (e.g., guanethidine, methyldopa, clonidine) may be reversed due to the inhibition of presynaptic uptake of the antihypertensive or the desensitization of alpha-2 receptors. Due to inhibition of presynaptic uptake, TCAs may increase the vasopressor response of direct-acting sympathomimetics (phenylephrine, epinephrine, and norepinephrine) and decrease the vasopressor response to indirect-acting sympathomimetics (e.g., ephedrine).

Concomitant use of TCAs and monoamine oxidase inhibitors (MAOIs) is generally not recommended due to potentially serious or fatal reactions including hypertensive crisis, hyperpyrexia, excitation, and convulsions. It should be noted that some refractory patients may be safely treated with this combination with enhanced efficacy relative to monotherapy. Similarly, the SSRIs, venlafaxine, nefazodone, bupropion, and mirtazapine should not be co-administered with MAOIs due to the potential for hypertensive crisis, serotonin syndrome, confusion, and delirium. MAOIs should be discontinued 2 weeks prior to starting a non-MAOI antidepressant. Likewise, when switching from a non-MAOI antidepressant to an MAOI, the non-MAOI should be discontinued for 2 weeks (5 weeks for fluoxetine due to long half-life) prior to starting an MAOI.

**Serotonergic antidepressants may cause a serotonin syndrome.**

MAOI antidepressant. Serotonergic antidepressants may cause a serotonin syndrome when combined with other agents that increase serotonin activity. Serotonin syndrome occurs as a result of an excessive drug-induced increase in serotonin transmission. Symptoms include cognitive behavioral changes (e.g., confusion, hypomania, agitation), autonomic dysfunction (e.g., diarrhea, fever, diaphoresis, changes in blood pressure, nausea, vomiting), and neuromuscular abnormalities (e.g., myoclonus, hyperreflexia, incoordination, tremor). Serotonin syndrome
has been reported with SSRIs when combined with MAOIs (including selegiline), lithium, L-tryptophan, buspirone, trazodone, carbamazepine, clomipramine, and other SSRIs. Additionally, SSRIs or MAOIs combined with certain opiate medications (e.g., meperidine, dextromethorphan, tramadol, and pentazocine) with serotonergic effects has resulted in serotonin syndrome. Symptoms of serotonin syndrome usually develop after the addition of another serotonergic drug or after a dosage increase of the serotonergic agent. Most patients respond rapidly to discontinuation of the serotonergic drug(s) and supportive care. Case report data suggest serotonin receptor antagonists may be beneficial if symptoms are severe or persist. Cyproheptadine has produced the most consistent effects, but methysergide, propranolol, and phenothiazines have also been used. Prevention strategies and early recognition of symptoms are important to prevent more serious or fatal outcomes of serotonin syndrome. Caution should be used with combination therapy of serotonergic agents.

CONCLUSIONS

SSRIs and the other newer antidepressants have changed the treatment of depression with their improved tolerability and safety profile. More patients are now being treated with antidepressants, in part due to the decreased burden these medications have on prescribers. As these drugs are widely prescribed in many different settings, the risk for pharmacodynamic and pharmacokinetic drug interactions increases. The risk for drug interactions as well as the resultant clinical sequelae should be considered when selecting an antidepressant. While some interactions may be tolerated by the patient or even go unnoticed by clinicians, many will require increased monitoring for safety and/or dosage adjustments. The role of the pharmacist in the process of identifying, preventing, and managing drug interactions is extremely important. Pharmacists should also play a vital role in educating physicians and other prescribers as our understanding of drug interactions changes rapidly.

REFERENCES

Strategies for Treatment Refractory Depression

Jessica L. Goren

Ten to thirty percent of patients do not respond adequately to antidepressant therapy. Absolute treatment refractory depression occurs in up to 10% of patients with depression. To date, few studies have addressed this issue. Several treatment options are available for refractory depression, including increasing the dose, extending the treatment period, switching and augmentation strategies, and electroconvulsive therapy. This paper will review some strategies available for treatment refractory depression.

KEY WORDS: refractory, depression, augmentation, switching.

INTRODUCTION

Acute and chronic depression is a common disorder, affecting approximately 5.7% of the population over the course of a lifetime.1,2 Women have a prevalence twice that in men.1,2 Despite adequate treatment, up to 30% of patients fail to achieve a satisfactory response after an initial trial with an antidepressant.3 The American Psychiatric Association’s practice guidelines for depression define an adequate treatment as a trial of therapeutic doses of an antidepressant for at least 6 to 8 weeks.3 Response criteria commonly cited in clinical studies include a 50% reduction in depressive symptoms on a standard rating scale, a rating of “much improved” on the clinical global impression scale, and/or an absolute score on a symptom rating scale.4 Treatment refractory depression has been defined as treatment nonresponse despite at least 2 adequate treatment trials with antidepressants from different pharmacologic classes.4 Interestingly, a large portion of “treatment refractory” patients referred to specialty treatment centers have not received an adequate antidepressant trial with even one agent.5,6 Thase and Rush proposed a system to rank the degree of treatment refractoriness (Table 1).4 These criteria help assess the degree of refractoriness, recognizing that not all treatment failures represent absolute nonresponse to treatment. Up to 15% of patients are only partial responders. Residual symptoms are associated with an increased risk of relapse, making treatment of this population particularly critical.4 Patients intolerant of antidepressant medications are not truly refractory. However, they present a unique treatment dilemma, because it is difficult to achieve the therapeutic dose necessary to obtain a response.4

DIFFERENTIAL DIAGNOSIS

When a patient presents with an inadequate response to antidepressant therapy, a review of their medical, psychiatric, and social history is necessary to rule out factors that reduce responsiveness to an antidepressant. This may include substance abuse; comorbid medical conditions, such as uncontrolled chronic pain; or comorbid psychiatric conditions, such as anxiety disorders or bipolar variants of mood disor-
It is also important to ensure compliance when assessing treatment response. Missed doses or self-discontinuation may be confused with inadequate response or lead to withdrawal syndromes which may mimic depressive symptoms. The most commonly cited reason for noncompliance is side effects. Thus, it is important to counsel patients about the importance of compliance for response and to match side effect profile to a patient’s lifestyle. Once alternate causes for nonresponse have been ruled out, patients should be ranked by the Thase and Rush criteria to see if their degree of treatment resistance warrants more complex medication trials. Many treatment options exist for treatment refractory depression. The more common options will be discussed in detail.

### EXTENDING TREATMENT TRIAL AND INCREASING DOSES

Selective serotonin reuptake inhibitors (SSRIs), bupropion, nefazodone, venlafaxine, desipramine, and nortriptyline are the agents considered most appropriate for first-line antidepressant therapy due to their relative safety and tolerability. Reservation of monoamine oxidase inhibitors is customary except in atypical depression.

Extending the current medication trial of any initial agent, with or without dosage increases, is a plausible initial treatment strategy. A lack of response should not be viewed as absolute before a minimum of a 4-week trial at therapeutic doses due to antidepressants’ delayed response. In light of this, antidepressant doses should not be increased before this interval has passed. Unfortunately, there is not enough data either supporting or refuting the utility of an antidepressant trial beyond 6 to 8 weeks. However, an extension of 2 to 4 weeks beyond an initial treatment trial may be especially useful in patients with personality disorders. Due to the safety of this strategy, it is an option for stage 1 refractoriness or a partial responder.

Practitioners are more likely to increase the dose of a serotonin reuptake inhibitor (82%) rather than switch agents in a partial responder. In support of this practice, a recent study demonstrated that after 8 weeks, partial responders may have more benefit from an increased dose compared with lithium or desipramine augmentation. Due to superior efficacy with increasing doses of bupropion, nefazodone, and venlafaxine, these agents may be most appropriate for an increasing dose strategy. Doses should be increased to maximally tolerated, nontoxic doses for a minimum of 1 to 2 additional weeks. Selective serotonin reuptake inhibitors’ relatively flat dose-response curve may make these agents less appropriate for increasing doses.

Potential disadvantages of increasing doses include increased side effect burden, increased cost, and a potential delay in instituting a therapeutic treatment. However, the American Psychiatric Association states an increase in dose may be associated with a modest response, making this strategy appropriate in stage 1 refractoriness.
SWITCHING ANTIDEPRESSANTS

Switching antidepressants offers several advantages compared with increasing doses and augmentation strategies. Primarily, patients may be frustrated with lack of effect and increased cost with increased doses. Drawbacks of switching include washout periods, discontinuation syndromes and potential loss of any therapeutic effect from the initial agent.

When a switch has been determined to be an appropriate strategy, two options are available: switching within the antidepressant drug class or switching to a different class. Patients intolerant or unresponsive to one agent may benefit from another agent within the same class with a different side effect profile or an agent from another class. Both switching within or between classes of antidepressants is most likely to be beneficial in stage 1 treatment refractoriness.

Switching within the Same Class

To maximize the potential benefit of switching within the tricyclic (TCA) class, one should consider that amitriptyline and imipramine are metabolized to nortriptyline and desipramine. Clomipramine may represent a unique TCA due to its potent inhibition of serotonin reuptake and may be useful despite previous failure with TCAs.

There is a 10%–30% response rate with a within-class TCA switch in previous nonresponders. Within-class switching of SRIs represents a better-tolerated and safer therapeutic option compared with TCAs. Studies have demonstrated that 40%–70% of patients unresponsive or intolerant to one SRI can respond to an adequate trial of a different SRI. A complete lack of response to 8 weeks of fluoxetine is better managed with switching to an agent from another class. The different pharmacologic profiles of heterocyclic agents (HCA) does not truly represent a switch within one class.

At this time, the strongest evidence supports in-class switching in a patient with a stage 1 or 2 refractoriness or partial response.

Switching with a Different Class of Antidepressant

Due to the number of pharmacologically different antidepressants, many switches are possible between classes. TCAs, SRIs, and HCAs have all been demonstrated to be effective alternate antidepressants in nonresponders. Current clinical practice seems to indicate that this is the preferred treatment in nonresponders. The choice of a different antidepressant should be based on past medical history, concurrent medications, adverse effect profile, and patient preference. In a recent study of SRI users, demonstrated practitioners prefer to switch to a non-SRI (44%) rather than another SRI (17%) in nonresponders.

Switching of TCA nonresponders to SRIs, bupropion, or venlafaxine has been shown to be an effective treatment. Monoamine oxidase inhibitors (MAOIs) are typically reserved for atypical depression. A review of the literature demonstrated TCAs’ efficacy in both SRI and MAOI nonresponders. Venlafaxine response has also been demonstrated in SRI treatment–resistant patients. In light of data demonstrating that venlafaxine has a 10% increased remission rate over SRIs, it may convey some unique benefits in an SRI-resistant population. Other studies have demonstrated MAOIs’ effectiveness in atypical and bipolar depression.

Data supports a switching with a different class of antidepressant in stage 1 or 2 refractoriness. Choice of a preferred agent for a switch is based on medical history, concurrent medications, and adverse side effect profile and drug interaction burden. Preferred substitution for SRI nonresponders includes an alternate SRI, bupropion, venlafaxine, or nefazodone. Use of a TCA or venlafaxine may be particularly advantageous in patients who worsen during treatment with an SRI. Patients with atypical depression who have been treated with an SRI may benefit the most from an MAOI, while SRIs may be most beneficial in atypical depression initially treated unsuccessfully with a non-SRI.
COMBINATION MEDICATION THERAPY

In an effort to increase compliance, decrease side effects and cost, and eliminate the risk of drug interactions, monotherapy is the preferred initial treatment strategy for treatment refractoriness. However, a substantial portion of patients fail to respond to one agent. Thus, polypharmacy may be necessary to stabilize treatment refractory patients. Two options are available: combining antidepressants from different classes and augmenting an antidepressant with a nonantidepressant agent. Combination therapy will require the clinician to pay close attention to dosage to minimize adverse drug reactions and interactions. The advantages and disadvantages of these options will be discussed below.

**Monotherapy is the preferred initial treatment strategy for treatment refractoriness.**

**COMBINATION ANTIDEPRESSANTS**

As antidepressants become more selective in their pharmacologic actions, combining antidepressants with different pharmacologic properties is a rational option for treatment refractoriness. For example, a secondary TCA with an SRI offers noradrenergic and serotonergic effects, while the addition of an MAOI would add dopaminergic effects. Data frequently do not support or refute the benefit of any one particular combination, and direct comparisons are rare. This puts the responsibility on the clinician to base antidepressant choice on the patient’s past antidepressant response, concurrent medical conditions, and potential adverse events. Just a few of the adverse events reported in the literature from combination antidepressant therapy include serotonin syndrome, panic attacks, and agranulocytosis.

Studies of SRI/TCA combinations have demonstrated a 25%–65% response rate. Some combinations that have been studied include fluoxetine treatment with desipramine, imipramine or nortriptyline, as well as sertraline and imipramine. Treatment populations have included patients who have failed up to 2 trials of monotherapy or at least 1 augmentation trial. One open-label study demonstrated a rapid response in patients receiving a SRI and TCA combination. This effect may be attributable to SRIs’ potential to increase serum TCA concentrations. Since toxicity correlates with higher serum concentrations, monitoring of TCA serum levels is advisable. High TCA serum levels may increase cardiac toxicity, and close monitoring is necessary. Due to paroxetine’s and fluoxetine’s potent inhibition of cytochrome P450 2D6 enzyme system, these agents are more likely to increase levels of TCA serum levels. Due to the lack of rigorous studies, TCA/SRI combinations may be more useful to patients who are stage 3 refractoriness.

Increased risk of serotonin syndrome and hypertensive crisis makes close monitoring essential when using combinations involving MAOIs with TCAs and contraindicated with MAOI/SRI combinations. The data supporting the efficacy of TCA/MAOI combinations is mixed. Should this strategy be used, it is safer to add the TCA to an established MAOI regimen. Newer antidepressants have little data to support or refute their use in combinations with MAOIs in treatment refractory patients. Pierre and Gitlin reported that the efficacy of the combination of bupropion and tranylcypromine was effective in one treatment refractory patient. With this combination, the risk of hypertensive crisis is increased; thus, compliance with the MAOI diet is essential. Due to potential risks with MAOI combination therapy, it should probably be reserved for stage 5 refractoriness under the supervision of a psychiatrist after safer strategies fail.

Data with the newer antidepressant combinations are not controlled and consist primarily of case reports. Combinations reported as effective for the treatment of refractory depres-
sion with bupropion include sertraline, paroxetine, and venlafaxine. Potential advantages of combining newer agents include treatment of side effects associated with the initial antidepressant. Nefazodone and bupropion have both been used to reverse sexual dysfunction associated with SRI use. Potential disadvantages include serotonin syndrome reported with nefazodone/paroxetine and venlafaxine/fluoxetine combinations, as well as a report of panic with bupropion/fluoxetine treatment and agranulocytosis with mianserin/venlafaxine combinations. Due to a paucity of blinded, controlled data demonstrating the combination of these antidepressants as superior to monotherapy with broad spectrum antidepressants, the role of the combination of newer antidepressants in treatment refractory depression remains unclear and reserved for when more established therapies such as TCA/SRI combination or augmentation strategies fail.

**The role of the combination of newer antidepressants . . . remains unclear and reserved.**

**AUGMENTATION STRATEGIES**

The main advantage of augmentation over switching is avoidance of exacerbation during the taper of the first antidepressant. In addition, some data indicate a quicker acceleration of response time with augmentation strategies. The disadvantages include increased risk of adverse drug reactions, drug interactions, and higher cost.

Augmentation strategies are indicated after complete nonresponse to a 4-week trial of an antidepressant with standard doses, then an additional 1 to 2 week trial of maximally tolerated doses. Lithium, thyroid supplementation, stimulants, pindolol, anticonvulsants, and anxiolytic agents are among the augmentation strategies reported in the literature.

**Lithium Augmentation**

Lithium is the most extensively studied augmentation strategy for treatment-resistant depression. A recent meta-analysis supported previous findings that lithium augmentation significantly improves response rates compared to placebo. The meta-analysis included only double-blind, placebo-controlled studies and found the absolute improvement in response rate was 27%. An odds ratio of 3.31 favored lithium-treated patients compared to placebo-treated patients.

Another study addressed the issue of duration of augmentation therapy necessary to prevent relapse. Findings of the study demonstrated an increased risk of suicide and relapse in patients who discontinued lithium augmentation after 2 to 4 weeks when compared to continued lithium treatment for 6 months. Thus, in the absence of contradictory evidence, a 6-month period of lithium augmentation should be the minimal duration of treatment. Serum concentrations between 0.5–1.0 meq/liter have been associated with response. Lithium augmentation is considered by many experts to be first-line treatment after failure of mono-therapy. Due to extensive studies of lithium augmentation, it should be used in stage 2 or 3 refractoriness.

**Thyroid Augmentation**

Thyroid augmentation has been well studied and offers the advantages of relatively few adverse drug reactions and is generally well tolerated. While L-triiodothyronine (T₃) in doses of 20–30 µg a day is typically used rather than thyroxine (T₄), there is data to support use of both agents. L-Triiodothyronine has demonstrated efficacy in euthyroid patients and treatment refractory patients and has hastened antidepressant response. Thyroxine, in doses of 150–300 µg a day, has more data to support its use in treatment-resistant bipolar disorders. Thyroid supplementation is extensively studied and should be used for stage 3 refractoriness after lithium augmentation.
fails. It should be considered first-line treatment for any patient with borderline or subclinical hypothyroidism.

**Pindolol Augmentation**

Pindolol, a β-blocker, is also a potent inhibitor of the presynaptic 5-HT$_{1A}$ autoreceptor. Pindolol treatment may prevent the auto-receptor-mediated down-regulation of antidepressants that inhibits serotonin reuptake and thus hastens the antidepressant effect.

Several trials have addressed the use of pindolol augmentation for increased response rate as well as acceleration of antidepressant response. The trials designed to demonstrate pindolol’s impact on accelerating antidepressant response have primarily been positive. The majority of studies found pindolol effective for hastening onset of action of antidepressant therapy with fluoxetine, fluvoxamine, and nefazodone. One study has shown no acceleration of effect. The data for pindolol augmentation of antidepressant efficacy has been mixed. Response rates to trazodone, paroxetine, fluvoxamine, imipramine, and phenelzine were increased in patients not responding to SRIs, MAOIs, or who failed up to 2 trials with other augmentation strategies. Patients who failed lithium, desipramine, or buspirone augmentation improved after the addition of pindolol. Other studies failed to document pindolol as an effective augmentation strategy. Doses of 7.5–10 mg a day have been reported. Pindolol is used as an agent to accelerate response when a fast onset of action is desired. Due to conflicting findings, pindolol augmentation agent should be reserved for patients who have failed more established augmentation strategies.

**Buspirone Augmentation**

Similar to pindolol, buspirone acts at 5-HT$_{1A}$ autoreceptors as well as postsynaptic dopamine D$_2$ receptors. Buspirone monotherapy at doses of 45–60 mg/day has demonstrated antidepressant activity. Unlike pindolol, there are no data to support the theory that buspirone hastens the antidepressant response. The data to support buspirone’s efficacy as an antidepressant are sparse but consist primarily of blinded and/or placebo-controlled trials with approximately 150 subjects per trial. The data supporting buspirone’s effectiveness as an augmentation of SRI treatment are mixed. The only large, randomized, placebo-controlled trial failed to demonstrate buspirone’s efficacy as an augmenting agent over placebo in SRI-treated patients. Due to the paucity of data and a large negative trial, buspirone augmentation should be reserved for patients who have failed other treatments.

**Alternate Medication Strategies**

Anticonvulsants, anxiolytics, and stimulants have all been studied as augmentation strategies in treatment refractory depression. Several studies have addressed carbamazepine use as an antidepressant and an augmentation for treatment refractory and chronically depressed patients. Due to its potential for drug interactions and limited data, this therapy is best reserved for later stages of stage 5 refractoriness. Valproate may also interact with antidepressants and has even fewer data to support its use compared with carbamazepine. Valproate appears to be a more effective antimanic agent as opposed to antidepressant. Valproate’s main role is in the long-term prophylaxis of bipolarmania. Valproate’s role in treatment refractory depression remains unclear and should only be used as a last resort at this time.

It has been shown that 33%–41% of patients taking SRIs were also taking concomitant sedative or hypnotic treatments. Benzodiazepines are effective in treating some of the signs of depression such as anxiety and altered sleep patterns, especially before the antidepressant starts working. However, there is no substantial literature to demonstrate their ability to treat depression as monotherapy or treatment refractory depression. Benzodiazepines are best used in depression to reduce early insomnia, anxiety from the disease, and antidepressant-induced...
insomnia. Benzodiazepines are not indicated for treatment refractory depression unless a comorbid condition exists that can be effectively managed by this drug class.

Methylphenidate and amphetamine have been evaluated as augmentation strategies with SRIs, TCAs, and MAOIs. A small case series has recently reported modafinil as an effective augmentation strategy, especially in patients with fatigue. Current paucity of data only supports the use of stimulants in anergic and treatment refractory depression in stage 5 treatment refractoriness.

**ELECTROCONVULSIVE THERAPY (ECT)**

ECT should be considered for anyone with moderate to severe treatment refractory depression due to its safety, efficacy, and long history of clinical experience. ECT is more effective than many combination therapies with up to 50% of medication-resistant patients responding. The most problematic complications from ECT are cognitive disturbances, especially short-term memory impairment and a headache in the period immediately after the ECT treatment. Traditionally, after a course of 6–12 ECT treatments, prophylaxis medication or maintenance ECT is required to prevent relapse. A recent study found an 84% relapse rate in patients receiving placebo after completion of a successful trial of ECT. Patients who were maintained on nortriptyline or lithium plus nortriptyline for 24 weeks had a relapse rate of 60% and 39%, respectively. The study underscores the need for continued treatment after a course of ECT and suggests combination antidepressant and lithium treatment is more efficacious than antidepressant monotherapy. ECT is typically reserved for patients with stage 4 refractoriness.

**CONCLUSIONS**

Lack of response to first-line treatments in depression is a common problem and is usually a function of external factors such as noncompliance and inadequate antidepressant trials. Numerous strategies for true treatment resistance are available. Most clinicians manipulate the dose of the initial medication or switch to a new medication before trying combination therapy. There is limited research into the efficacy of most of the strategies alone and in comparison to each other. Use of Thase and Rush’s criteria to stage treatment refractoriness is a useful first step in evaluating the severity of the problem and giving structure to the decision about which therapy to use first. Treatment should be initiated with the safest therapies that have the most data supporting their use, such as switching classes, combination of SRIs with TCAs, and lithium and thyroid augmentation. Other strategies, such as combination of new agents and stimulant augmentation, should be reserved until after these treatments fail.

**REFERENCES**


49. Spier SA. Use of bupropion with selective serotonin reuptake inhibitors and venlafaxine. Depress Anxiety. 7: 73–75.
73. Blier P, Bergeron R. Effectiveness of pindolol with selected antidepressant drugs in the treatment of ma-
Management of Depression in Children and Adolescents

Julie A. Dopheide

Depression is increasingly recognized as an illness that causes functional impairment and diminished quality of life for all age groups, including children. One to two percent of children and between 4% and 8% of adolescents meet Diagnostic Statistical Manual of Mental Disorders (4th ed.) (DSM-IV-TR) criteria for major depression. Psychotherapy, particularly cognitive-behavioral therapy, is effective, with 70% response rates. Antidepressants are effective according to limited controlled trials; however, concern exists over the gap between research and clinical practice, as most antidepressants are not well-studied in youth. Nevertheless, pharmacotherapy has gained greater acceptance in pediatric psychiatry, and prescriptions for antidepressants in youth have increased dramatically over the past 5 to 10 years. In 1995, 1.08 million selective serotonin reuptake inhibitor prescriptions were written for children and adolescents. Scientific evidence for the safety and effectiveness of antidepressants in youth is reviewed along with data on nondrug interventions such as cognitive-behavioral therapy. Recommendations for promoting the safe and effective management of depression in children and adolescents is provided.

KEY WORDS: child, adolescent, depression, cognitive, antidepressant.

INTRODUCTION

As troubled youth capture news headlines with school-yard shootings and increasing rates of homicide and suicide, society is left with many questions. Could this have been prevented? Is it psychiatric illness? Are psychiatric illnesses appropriately recognized and treated in children and adolescents? What treatments are safe and effective for youth? Clearly, there are many factors that contribute to behavioral, thought, and mood disturbances in youth who commit these violent acts (substance abuse, psychosis, trauma, severe family dysfunction, etc.). One increasingly recognized factor is depressive illness. Untreated depression can impair school performance and negatively affect social and family relationships and contribute to the risk of substance abuse. This paper will address differences in the clinical presentation of depression in children and adolescents, discuss risk factors and associated conditions, and present evidence-based recommendations for managing depression in youth.

EPIDEMIOLOGY

Depressive disorders affect 0.3% of preschoolers, 2% of elementary school-age children, and between 5% and 8% of adolescents. Prepuberty rates of depression are similar in boys and girls; however, depression is more common in females postpuberty, implying hormonally influenced symptom expression. Whenever depression presents, a thorough diagnostic assessment is critical to identify all contributing factors and comorbid medical and psychiatric disorders. For example, if depressive symptoms are clearly environmentally...
based, a medication may not be useful and only puts the child at risk for adverse effects. Conversely, if psychotic symptoms are missed and only nonpharmacologic treatment is implemented, the child may be at greater risk for suicide.1

DIAGNOSTIC ASSESSMENT

Accurate and comprehensive assessment of youth must include an objective assessment of the child by the clinician and collateral information from multiple informants, including parents, teachers, siblings, and extended family. Symptom checklists such as the child behavioral checklists (CBCL) and rating scales such as the Children’s Depression Rating Scale—Revised (CDRS-R), the Child Depression Inventory (CDI), and the Beck Depression Inventory (BDI) are useful in gathering objective information on symptoms of depression.10–13 This is crucial given the reactivity of depressive symptoms in children and their susceptibility to environmental influences.13

Children and adolescents with major depression meet DSM-IV-TR criteria for major depression in adults but have the following differences in their clinical presentations. Depressed children (5–8 yrs) are less able to verbalize emotions and present with more vague somatic complaints (“my tummy hurts,” “I don’t feel good”). Behavioral disturbances are also common, such as outbursts of crying, shouting, unexplained irritability, or lack of interest in playing with friends. Older children (9–12 yrs) begin to talk about running away from home, boredom, low self-esteem, guilt, hopelessness, and fear of death. Adolescents have more sleep and appetite disturbances; they may exhibit reckless behavior, exhibit poor school performance, have difficulty in relationships, and may present with delusions, irritability, and suicidal ideations and attempts.4,14

Similar to adults with depression, a high degree of hopelessness predicts suicide attempts, while the ability to cognitively identify reasons for living is protective against suicide.2,14

ETIOLOGY AND CLINICAL COURSE

Risk factors for developing depression include genetic predisposition, substance abuse, and psychosocial stressors (e.g., maternal mental illness, lack of paternal communication, unsafe living conditions, physical or sexual abuse) or parental loss through death or divorce.4,6 Most studies report a more protracted course of lifetime depressive illness with onset during childhood or adolescence.15 However, newer evidence suggests that depression with an onset in adolescence may be a different disorder than that which starts in childhood.9,16,17 The heritability of depressive symptoms may be greater in adolescents than in children,9,16–18 and adolescents with major depression may be more likely to have depressive relapses into adulthood compared to child-onset depression.9,16,19

COMORBIDITY

A depressed youth with no other psychiatric diagnosis is a rarity. Common comorbid conditions include attention deficit–hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), bipolar disorder, substance abuse, schizophrenia, dissociative states, and trauma-related “hallucinations.”4 The presence of multiple comorbid conditions and psychosocial stressors increases the severity and chronicity of the depressive episode.6,9,13,19 One theory is that certain psychiatric diagnoses occur on a continuum and may be caused by related brain pathophysiology which may be genetic and/or environmentally mediated.13 Clearly, more research is needed, but when considering the causes of depression, it is not “nature or nurture” but “nature and nurture.”

TREATMENT

As with adults, treatment options include interpersonal psychotherapy (IPT), cognitive behavioral therapy (CBT), light therapy, and
antidepressant medication. Treatment should be implemented whenever depressive symptoms persist and impair functioning. Treatment selection is based on the severity of illness, comorbid conditions, patient/family preference, and access to care. There is no single superior treatment for depression in all children and adolescents. When comparing efficacy of treatments, IPT is as effective as medication for mild to moderate depression in youth. CBT is superior to IPT and other non-specific psychotherapeutic interventions such as supportive, psychodynamic, and family therapy in relieving symptoms of nonpsychotic major depression according to 8–10 week controlled clinical trials. CBT response rates are 70% across some trials. IPT focuses on problem areas of grief, interpersonal roles, transitions, and disputes. CBT teaches patients to identify and counteract distortions in the way they view themselves and their circumstances. Therapists qualified to provide IPT and CBT range from well-supervised novice social workers and occupational therapists to experienced child psychologists and psychiatrists.

One study contends that younger children with less severe depressive symptoms and less psychosocial impairment may be more responsive to psychotherapeutic interventions. Longitudinal studies assessing CBT and IPT with regard to relapse prevention are needed.

Seasonal affective disorder (SAD) can occur in children and adolescents, typically during dark winter months. The American Academy of Child and Adolescent Psychiatry (AACAP) recommends bright-light therapy as first-line treatment for SAD due to established efficacy and good tolerability. The most widely used treatment is a light box placed one foot in front of the child’s face for 30 min per day, preferably in the morning. Treatment can be extended to 1 hr in cases of partial response. Twenty-five hundred lux of light can be initiated in children < 9 yrs of age, while older children should receive a trial of 10,000 lux of light therapy. Onset of therapeutic effect typically occurs in 1 to 2 weeks. More studies are needed to determine the best duration of treatment; however, treatment is usually continued for the entire season.

Over the past decade, there has been a dramatic increase in the number of antidepressant prescriptions written for children. A U.S. study of two Medicaid databases from the Midwest and Midatlantic states and one HMO in the Northwest (U.S.) found higher prescribing rates in youth for all categories of psychotropics (stimulants, clonidine, antidepressants, anticonvulsants) between 1991 to 1995 compared to previous years. Antidepressant prescribing rates doubled in preschoolers, and they were the second most commonly prescribed class after stimulants. Selective serotonin reuptake inhibitors (SSRIs) replaced tricyclic antidepressants (TCAs) as the antidepressant most commonly prescribed for most age categories; however, preschoolers continued to receive TCA prescriptions presumably for enuresis and/or ADHD. Another U.S. study reports that in 1995, 1.08 million prescriptions were written for SSRIs to treat children with emotional disturbances including depression. In 1996, there was a 500% increase in the number of fluoxetine prescriptions in children aged 5 and younger.

Increasingly, children receive SSRI prescriptions from family practitioners and pediatricians for a wide array of indications that include depression, OCD, and ADHD. The therapeutic outcome of generalists prescribing compared to psychiatrists is unknown; however, referrals to psychiatric specialists are decreasing as generalists are increasingly comfortable prescribing SSRIs for youth. The AACAP argues against this practice, stating...
that clinicians specially trained in pediatric psychiatric assessment are best able to consider developmental and cultural factors in symptom presentation and develop a reliable differential diagnosis.

Given the increased prescribing of antidepressants, particularly SSRIs, to youth of all ages, it is important to consider the evidence for safety and efficacy of each antidepressant class in youth. Pediatric antidepressant dosing is not well established, but prepubertal children have accelerated hepatic metabolism compared to adolescents, and effective doses for children and teens often fall within established adult dosing ranges.6,7,29

SSRIs

When pharmacotherapy is indicated due to severity of symptoms, lack of response to nonpharmacologic treatment, or patient/family preference, then treatment with an SSRI is considered first-line due to established efficacy in controlled clinical trials (fluoxetine), a lack of controlled data for other nontricyclic antidepressants, and safety concerns with TCAs.4,5

Two double-blind, placebo-controlled studies evaluated fluoxetine therapy in children and adolescents with major depression. The larger study (n = 96) showed 27/48 or 56% of patients (aged 8–18 yrs) were rated at much or very much improved on fluoxetine at doses between 10 and 40 mg/day compared with 16/48 or 33% taking placebo (P < .02). Results were significant on the CDRS by week 5 of the 8-week study.27 A separate double-blind controlled trial showed trends toward improvement but no significant efficacy versus placebo when fluoxetine 20–40 mg/day was given to 40 adolescents (aged 13–18) over 8 weeks.28 Sertraline and paroxetine have demonstrated efficacy in published open trials in children and adolescents with general response rates ranging from 65%–75%.29,30 There is no evidence to suggest that one SSRI is more effective than another for youth. However, clinically, some physicians prefer fluoxetine and sertraline compared to paroxetine due to less anticholinergic activity and less risk of serotonin withdrawal reactions compared to paroxetine, an agent with no active metabolites.26 There is a paucity of data for citalopram and fluvoxamine in pediatric depression.

There are no SSRI dosing guidelines in youth. The available literature recommends empirical dosing based on the age and size of a child. Prepubertal children should be started at the low end of the dosing range; for example 10 mg of fluoxetine or paroxetine and 25 mg of sertraline with titration upward after 3 to 4 weeks depending on efficacy and tolerability.4,27–29 Adolescents more than 50 kg or 110 lbs can be started at typical adult doses and titrated accordingly. Response usually occurs between 3 and 6 weeks.4,27,29,30.

The adverse effect profile of SSRIs in children is, overall, similar to that found in adults with only a few exceptions. SSRIs may have a greater risk of behavioral activation in youth (20%–50%) compared to adults (2%–10%).4,26,31 “Behavioral activation” ranges from restlessness, jitteriness, and insomnia to frank mania. If these symptoms develop, the SSRI should be discontinued and the patient observed for resolution of symptoms. Abrupt discontinuation is needed for clear mania; otherwise, tapering over 1 to 2 weeks is recommended.4,6,26,31 If symptoms resolve, an alternative SSRI may be considered at a lower dose with slow titration and monitoring for re-emergent behavioral activation. If hypomania or mania persists after discontinuing the SSRI, a mood stabilizer may be needed.5,32 Controversy exists over whether underlying bipolar disorder is exposed by the SSRI or whether the behavioral activation constitutes a separate drug-related effect on younger, more reactive receptors.4,26,31 Both explanations are plausible, and the clinician should be open to the possibility of either. A diagnosis of bipolar disorder requiring mood stabilizer therapy is more likely if hypomania or mania persists 1 to 2 weeks after the drug has cleared from the body and if there is a family history of bipolar disorder.32

Other typical SSRI adverse effects (nausea, diarrhea, headache, and sexual changes) can
occur in children and adolescents and require monitoring and management.\textsuperscript{4,26,31} SSRI adverse effects are generally not dangerous and are manageable. Their lack of cardiovascular toxicity\textsuperscript{33} and relative safety in overdose compared to TCAs provides further evidence toward first-line therapy status in children and adolescents.\textsuperscript{5} More serious adverse events such as extrapyramidal symptoms and bleeding have been associated with SSRI therapy in children. Acute dystonia has been reported in children receiving SSRI alone and in combination with haloperidol or pimozide.\textsuperscript{26} SSRI-associated bleeding has been reported in 5 children, aged 8–15, who developed bruising or epistaxis 1 week to 3 months after starting SSRI treatment.\textsuperscript{34} There is no way to predict who will develop these reactions, so patient and family education with careful clinical monitoring is essential.

**TCAs**

TCA therapy is considered when at least two adequate trials of safer agents like SSRIs have been completed. Controlled trials show no significant difference for TCAs versus placebo in the treatment of depression in children and adolescents.\textsuperscript{4,5,7} Limitations of TCA trials include small sample size, possible subtherapeutic doses, and high placebo response rates. Therefore, risks of TCA therapy outweigh potential benefits for most children with depression, particularly with combined pharmacotherapy and the risk of drug interactions.\textsuperscript{5,35,36}

The cardiovascular toxicity of TCAs is well established. Increases in pulse and diastolic blood pressure and prolongation of the PR, QRS, and QT intervals are well documented in pediatric patients receiving TCAs.\textsuperscript{7} To further clarify the effects of TCAs on sympathetic and vagal modulation of heart rate variability, 75 children and adolescents (mean age 10.5 yrs) taking various psychotropics, including TCAs, were studied.\textsuperscript{36} Vagal modulation of heart rate was significantly impaired in TCA-treated children, resulting in unchecked sympathetic modulation of cardiovascular functioning and increased risk of tachyarrhythmias.\textsuperscript{36} When TCAs are administered to youth, electrocardiograms and vital sign monitoring are mandatory at baseline, after each dosing increase, and biannually thereafter.

Pediatric TCA doses are generally between 1 and 3 mg/kg/day, and doses should not exceed 5 mg/kg/day due to unacceptable risk of cardiotoxicity.\textsuperscript{6,7,15} Since 1990, there have been 7 reported cases of sudden death in children treated with TCAs, namely, desipramine and imipramine.\textsuperscript{7,35,36} Nortriptyline is the preferred TCA due to relatively less orthostasis and established therapeutic and toxic plasma levels.\textsuperscript{37} Steady state nortriptyline levels above 60 ng/ml are recommended for an adequate therapeutic trial, and levels above 300 ng/ml increase risk of anticholinergic and cardiovascular toxicity.\textsuperscript{6,15,36,37} TCA withdrawal reactions including nausea, emesis, diarrhea, diaphoresis, chills, malaise, and muscle aches are particularly problematic for children. When discontinuing TCA therapy, tapering over 7–14 days is recommended to minimize discomfort.\textsuperscript{37}

**OTHER ANTIDEPRESSANTS**

One 6-week, double-blind, placebo-controlled trial of venlafaxine immediate-release was conducted in 33 outpatients between the ages of 8 and 17 years who met DSM-IV criteria for major depression.\textsuperscript{38} Children in both groups received weekly ratings on CBCL, CDRS, HAM-D, and the CDI in addition to psychotherapy, which was primarily cognitive/behavioral. Each weekly session consisted of 45 min of individual and 15 min of collateral therapy. Depressive symptoms improved significantly over 6 weeks on all rating scales, but there was no statistical difference between venlafaxine and placebo groups. Doses were as follows: 37.5 mg/day in children 8–12 yrs old and 75 mg/day in older adolescents. Low doses and short duration of treatment may have contributed to a lack of detectable drug effect.
Mania occurred in one venlafaxine-treated patient as compared to none in the placebo group. Significant nausea was reported in 7/16 venlafaxine-treated patients as compared to one patient in the placebo group. It is unknown if extended-release venlafaxine would have resulted in less nausea. Adolescents treated with venlafaxine had significantly increased appetite as well. Improvement in depressive symptoms was likely related to weekly therapy and contact with clinician. Venlafaxine requires further study in children and adolescents.

Nefazodone is not well studied in children and adolescents. One open trial in 7 treatment-refractory children (mean age 12.4) with multiple comorbidity (ADHD, bipolar-mixed, anxiety disorder) describes 4/7 children as much or very much improved with the use of nefazodone. The mean daily dose was 357 mg/day, and the study continued for 13 ± 8 weeks. Interestingly, 2/4 bipolar patients were among the responders, and two were considered non-responders and developed a mild mania. Morning somnolence was the only other reported adverse effect experienced by one child. Nefazodone may be a useful adjunct to treat depressive symptoms in youth with comorbid conditions, but more studies are needed.

Bupropion is an antidepressant with selective noradrenergic and dopaminergic activity. Currently, there are no published controlled clinical trials establishing efficacy for children and adolescents with depressive illness, but open trials demonstrate efficacy and safety for adolescents with conduct disorder, substance abuse, and ADHD with or without comorbid depressive illness. Dosing is not established for youth, but available trials report doses between 100 and 400 mg/day of the immediate release or sustained release preparation. Dosing should be divided bid in most cases, with gradual titration over days to weeks to minimize risk of seizures. Bupropion should not be used if the child has a seizure disorder or a history of seizures. Insomnia or sleepiness, agitation, rash, headache, and nausea are all possible when bupropion is administered to children and adolescents. Youth should receive careful monitoring for the development of tics, which have been reported in children treated with bupropion.

While mirtazapine is currently prescribed in youth, there are no published reports describing efficacy and tolerability.

In response to the lack of controlled data in treating mood and other psychiatric disorders in youth, the National Institutes of Health (NIH) have developed pediatric psychopharmacology research networks to focus on the safety and efficacy of currently available psychotropics in children. One NIH-funded study, the Treatment for Adolescents With Depression Study is underway. In addition, the FDA now mandates that children be included in all new drug entity studies of human subjects when it seems likely that the drug may be used in children.

**FDA now mandates that children be included in all new drug entity studies of human subjects.**

**COMBINATION PHARMACOTHERAPY AND DRUG INTERACTIONS**

Combined pharmacotherapy is increasingly used given multiple comorbid conditions typical of youth with depressive disorders. While combined pharmacotherapy is appropriate in some children, it is largely unstudied and increases the risk for adverse effects and drug interactions. A systematic approach to medication introduction with objective ratings of response is essential, given high initial placebo-response rates and multiple contributing factors in recovery. Whenever multiple comorbid conditions exist, the predominant illness should be treated first, with ongoing assessment to determine if an additional medication is necessary. For example, if ADHD and major depression coexist but ADHD is the dominant disorder, then stimulant monotherapy should
be introduced. If depressive symptoms resolve, then there is no need for additional medication. If ADHD symptoms remit but depression continues, then an SSRI may be added to the stimulant or bupropion may be tried in place of the stimulant. If lack of efficacy is documented, then the medication can be tapered off. If partial response is clear, then another suitable medication can be introduced.\textsuperscript{5}

Drug interactions are a primary concern in children, as there are limited formal studies assessing the nature and significance of these interactions in youth. One potentially dangerous interaction seen in children treated for depression involves TCAs and psychostimulants. Stimulants can increase TCA plasma levels.\textsuperscript{44} In addition, increased sympathetic tone from the stimulant and blocked vagal regulation caused by TCAs can result in unop-

**Drug interactions are a primary concern in children.**

posed sympathetic activity that can cause toxicity; death has been reported.\textsuperscript{35} SSRI and stimulant combinations are increasingly used. While more research is needed, SSRIs that inhibit 2D6 (fluoxetine and paroxetine) can cause increased amphetamine plasma levels, which may increase adverse effects/toxicity.\textsuperscript{44} This pharmacokinetic interaction may be less likely when methylphenidate is combined with SSRIs.\textsuperscript{44,45} Each child receiving combined pharmacotherapy needs an on-going assessment of the clinical impact of drug interactions.

**MONITORING**

Consistent follow-up is necessary to provide educational support for families/caregivers and to provide documentation of response and adverse effects.\textsuperscript{4,5} Once remission is achieved, patients should continue therapy for at least 6 to 12 months.\textsuperscript{4} Maintenance therapy may be needed to prevent relapse.\textsuperscript{4} Careful longitudinal care is more important than the initial drug selection. While longitudinal studies in the treatment of depression in children are lacking, the 14-month MTA study in children treated with stimulants for ADHD taught several lessons that likely apply to treating other psychiatric diagnoses, including depression.\textsuperscript{46,47} The study found that community care that included stimulant therapy but lacked consistent follow-up support was significantly less effective than stimulant therapy that included regular contact with the clinician.\textsuperscript{46,47} Stimulants are well established as the most effective treatment for ADHD, yet they were ineffective in a community care model that could not ensure regular follow-up and contact with clinician. Consistent follow-up allows for reaffirmation of treatment adherence, ongoing adverse effect management, dosage adjustments, and support for caregivers.

**PATIENT/FAMILY EDUCATION**

An effective medication education strategy is necessary to make sure that all involved family and caretakers understand the role of medication and the importance of treatment adherence. For example, one parent may send a positive endorsement of medication, while the other parent refuses to administer medication to the child. A child may see medication as “proof” that they are defective. They may call themselves “crazy,” “bad,” or “stupid” as an explanation for why they are taking medicine, thereby increasing a sense of inadequacy. Children may be teased by others for taking medication, reinforcing the belief that they are crazy or defective.\textsuperscript{48} Psychoeducation that includes the medical model for illness can be helpful in destigmatizing depression.
In summary, compared to adults, children and adolescents with depressive illness present with similar DSM-IV-TR symptoms (appetite and sleep changes, hopelessness, suicidal ideation) but may display more behavioral disorders and reactivity to their environment. Consequently, psychosocial interventions, which may include therapy for parents and family, are crucial to successful pediatric depression management.

Regarding treatment options in children and adolescents: CBT is a potentially successful treatment for nonpsychotic depression, while antidepressant therapy is indicated for moderate to severe depressive symptoms in youth who cannot participate in or do not respond to CBT. SSRIs are first-line antidepressants, because they are the most well studied and are generally safer and more effective than TCAs. Other antidepressants (venlafaxine, nefazodone, bupropion, or TCA) can be considered when SSRIs are either ineffective or poorly tolerated. A systematic approach with objective baseline and routine assessment of symptoms and side effects is needed, because youth have higher placebo response rates, and young children are less able to verbalize emotional responses and adverse drug reactions compared to adults.4–6

Special dosing and monitoring considerations for youth include gradual dosage titration of medication and gradual tapering off during discontinuation. Children have more hyperreactive autonomic nervous systems, are more prone to behavioral activation, and suffer significant withdrawal effects upon abrupt discontinuation of psychotropic medication.

REFERENCES
46. The MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for...

Geriatric Depression

Stephen C. Cooke and Melissa L. Tucker

Depression in the elderly is more common than once thought, especially in nursing home settings, where as many as 25% of residents can exhibit signs and symptoms of depression. Depression in the elderly can have a significant impact on overall health and desired outcome. The depressed elderly patient has been shown to have worsened prognosis of concomitant medical conditions, increased use of health care, decreased recovery time, and more likelihood to experience accelerated physical deterioration. Suicide represents the most serious complication of depression of the older depressed individual. The elderly are at a disproportionate risk for suicide attempts and are more likely to be successful. Diagnosis should be made using *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) (DSM-IV) criteria, and clinicians should use standardized rating scales such as the Geriatric Depression Scale to assist in monitoring the severity of depressive symptoms and the efficacy of antidepressant treatment. Several treatment options are available to the clinician and include psychotherapy, electroconvulsive therapy, older antidepressants such as the tricyclics, and newer more tolerable therapies such as the serotonin reuptake inhibitors. Drug therapy should be individualized and should take into account the pharmacokinetic and pharmacodynamic changes that are associated with normal aging.

**KEYWORDS:** depression, elderly, suicide, SSRI, pharmacokinetic, pharmacodynamic geriatric depression.

INTRODUCTION

Depression in the elderly is more common than once previously thought. Recognition and treatment of this disorder can be confounded by physiologic and psychological changes that are part of the normal process of aging. Depression in the elderly is associated with increased mortality, decreased quality of life, and worsened prognosis of accompanying medical disorders. Elderly depression is associated with an increased risk of completed suicide. Although many physicians and patients view symptoms of depression as an inevitable consequence of late life, both evidence and experts agree that depression is not a normal condition of the elderly. Depression causes more social disability than many other common ailments of late life such as diabetes, arthritis, back pain, hypertension, and cardiovascular disease. Adequate and efficacious antidepressant treatment strategies for late-life depression exist; however, recognition and assessment as well as provider education must be enhanced to improve the treatment of this disorder.

EPIDEMIOLOGY

Studies analyzed by the National Institutes of Health Consensus Panel on Diagnosis and Treatment of Depression in Late Life show that 15% of elderly individuals in community samples showed evidence of depressive symptoms.
Fully 3% met criteria for major depression. Of particular note and concern was the finding that elderly residents of nursing homes are at a disproportionately high risk, with a prevalence of major depression between 15% and 25% and an incidence of approximately 13% of new cases each year.

ASSOCIATED DISORDERS

Medical comorbidity is common and is associated with worsened disease outcome, increased health care use, decreased recovery time, delayed resumption of normal activities, and interference with treatment compliance. The relationship between cardiovascular disease and depression has been reported for over 60 years. Up to 30% of patients recovering from stroke experience depression. Almost 20% of patients who have had a recent myocardial infarction will meet criteria for major depression. Rates of coexisting depression in patients with coronary artery disease have been reported as high as 18%. In all of these groups, mortality is increased and overall prognosis is diminished as compared to patients who are not depressed. The relationship between cardiovascular disease and depression is confounded by several factors. Patients with depression have a higher rate of cigarette smoking, a known modifiable risk factor for cardiovascular disease. These patients are also less likely to succeed in smoking cessation efforts. However, several studies that controlled for smoking, as well as other cardiovascular risk factors, still showed an increase in ischemic heart disease in those study patients who were depressed. Some researchers have also hypothesized that increased cardiovascular risk is secondary to the use of tricyclic antidepressants (TCAs), a class of medications that is associated with slowed cardiac conduction, orthostasis, and fatal ventricular arrhythmias in overdose. This idea, however, was refuted in a well-designed study that showed that cardiovascular death rate was actually lower after the tricyclics became available.

Depression is common in patients with chronic pain syndromes such as cancer and rheumatoid arthritis. Up to 50% of patients with chronic pain will experience depression. Pain and depression are so intertwined that adequate antidepressant therapy can itself reduce severity of chronic pain. Current recommendations suggest that depression screens be routinely used during chronic pain evaluation and treatment.

Several neurological and psychiatric disorders have also been shown to be associated with depression. As many as one-fourth of Alzheimer’s patients will exhibit signs of depression. Parkinson’s patients appear to be at particular risk, with almost 50% experiencing depressive symptoms. Depressive episodes are also common in patients who have also been diagnosed with anxiety or substance abuse or who are experiencing withdrawal from substances of abuse, particularly cocaine.

COMPLICATIONS

Depression has been shown to accelerate physical deterioration in the elderly. A large study of community residents that assessed physical function over a 4-year period showed that depressive symptoms were predictive of loss of physical skills and self-care. This finding is especially important as individuals with declining self-care skills are at risk for nursing home placement. Adequate identification and treatment of these individuals may decrease subsequent admission to long-term care facilities.

The most severe and serious complication of depression, at any age, is suicide. Although they represent only 13% of the U.S. population, the elderly account for 25% of suicide attempts. In fact, elderly individuals account for the highest suicide rate among all age groups. By age 85, the suicide rate is over twice that encountered in the general population. Suicidal attempts in the depressed elderly patient are also more likely to be successful than in younger individuals. Tragically, opportunities for
intervention prior to suicidal attempts are often missed. A retrospective study of completed suicide revealed that 75% had seen their primary care provider within 1 month of death, 40% were seen within 1 week, and 20% were seen within 1 day.\textsuperscript{18} Simply put, failure to identify, diagnose, and adequately treat depression can have tragic consequences.

AGE CLASSIFICATION AND DEFINITIONS

Generally speaking, patients older than 65 have been traditionally defined as elderly. This nomenclature is, however, inadequate to describe the complete range of physiologic function encountered in a sample of older patients. Biologic variability in this population does not lend itself to precise numerical definitions of “elderly.” Some patients appear and are indeed elderly several years prior to the age of 65. Conversely, some patients in their seventh decade of life are physiologically and functionally much younger than their stated age. New terminology has been devised to clarify these differences. “Young old” describes a person between the ages of 60 and 74. The terms “very old” and “old old” are being used to describe individuals over the age of 75. “Oldest-old” describes an individual that is greater than 90 years of age. The term “frail elderly” describes an individual who is functionally older than he or she actually is.

ETIOLOGY

The etiology of depression in the elderly is thought to be influenced by both biological and psychosocial components. Biologic factors in the elderly, such as hereditary influence and neurotransmitter abnormalities appear to be similar to younger individuals with depression.\textsuperscript{19} Less similar to younger depressed patients, however, are the neuroendocrine and circadian rhythm changes that accompany normal aging. Dysregulation of the hypothalamic-pituitary-adrenal axis, long associated with the development of depression, increases with normal aging.\textsuperscript{20} In addition, older individuals experience changes in their circadian rhythm that affect sleep architecture to a similar degree as that seen in those with depression. Older patients exhibit increased periods of nighttime wakefulness, have more difficulty initiating sleep, and also experience decreased stage 4 and rapid-eye-movement sleep.\textsuperscript{21}

Many psychosocial causes of elderly depression have also been postulated. Although not clearly recognized as causative, these psychosocial factors should be identified and addressed in an effort to improve overall treatment and to possibly reduce or minimize future depressed episodes. According to one psychosocial theory, the development of a triad of negative beliefs regarding self-worth, current experiences, and a negative view of the future contribute to elderly depression.\textsuperscript{19} Stressors can also contribute to the development and severity of elderly depression. Stressful life events such as the loss of a spouse, onset of a major medical illness, retirement, and nursing home placement can herald the onset of a depression or worsen a depressive episode already in place. Other stressors associated with elderly depression include loss of mobility, decrease in independent decision making, loss of defining roles (“head of family”), debits in mental acumen, and loss of support and peer groups.

DIAGNOSIS AND EVALUATION

The diagnosis of depression in the elderly should be made using the DSM-IV criteria mentioned elsewhere in this series of articles. The presentation of symptoms in an elderly depressed patient may be similar to or may differ from a younger depressed patient.\textsuperscript{22} Elderly depressed patients may exhibit more cognitive impairment and social isolation and may complain less of dysphoric mood.\textsuperscript{23} The elderly may also be more somatically focused, experience a higher level of fatigue and psychomotor retardation, and complain more about loss
of interest in usual activities. Vegetative complaints such as decreased appetite and poor sleep may prompt initial contact with a clinician.

The elderly are at increased risk for comorbid medical conditions, and therefore, generally take more medications than younger patients. Many diseases and medications have been associated with causing or exacerbating depression. A comprehensive history regarding medical conditions and routine medications taken, including over-the-counter and herbal preparations, is invaluable at baseline to assist in differential diagnosis. As noted earlier, cardiovascular conditions such as stroke, coronary artery disease, and myocardial infarction have been closely tied to development of depression. Alzheimer’s and other dementias are also commonly linked to depression. Other diseases that should be ruled out or evaluated at the time of initial evaluation include thyroid abnormalities, diabetes, cancer, vitamin deficiency, fibromyalgia, inflammatory bowel disease, multiple sclerosis, and rheumatoid arthritis. The exact relationship between these diseases and depression is unclear. Some clinicians have hypothesized a direct connection between disease and neurotransmitter dysregulation. Others suggest that stress secondary to chronic illness may precipitate depressive symptoms in a susceptible elderly patient. Current treatment recommendations suggest treatment of both underlying illness and the depressive episode.

Medications that have been noted to worsen or cause depressive symptoms are numerous. Medications commonly used by the elderly such as steroids, diuretics, nonsteroidal anti-inflammatory agents, propranolol, methyl-dopa, and central nervous system depressants such as the benzodiazepines have been implicated in causing or worsening depressive symptoms.

A common occurrence for the elderly is bereavement over the loss of close friends or other family members. The process of grief or bereavement can resemble a major depressive episode. Generally, if bereavement lasts for more than a few months or if depressive symptoms become debilitating or severe, antidepressant treatment (either pharmacotherapy or psychotherapy) should be initiated. Patients should be reassured that antidepressant therapy does not interfere with the grieving process.

**PHARMACOKINETICS**

Pharmacokinetics is the study of a drug’s action within the body over a period of time. The various components of pharmacokinetics include the absorption, distribution, metabolism, and excretion of drug substances. These processes may change substantially due to physiological transformations that occur as a part of the aging process. These age-related changes are often unpredictable and vary from patient to patient (Table 1). In addition to increasing age, other factors such as comorbid disease states, multiple drug regimens, and environmental changes may further influence pharmacokinetic processes.

Alterations in pharmacokinetic processes in elderly patients are extremely important for clinicians to consider when prescribing agents for this population. Most antidepressant studies that have been conducted in the elderly population have only included healthy young-old patients. Therefore, the adverse effects reported in these studies have limited usefulness in patients who are elderly with multiple disease states and complex drug regimens. It is important for the clinician to individualize each patient’s overall physiological status (i.e., nutrition, hydration, cardiac output) and subsequently recognize how this status may affect the pharmacokinetic aspects of various medications. By individualizing each patient’s drug therapy, safer and more efficacious dosing regimens may be attained.

Absorption of most drugs occurs primarily in the small intestine via passive diffusion. Alterations in gastric motility, gastric emptying, and gastric pH are just a few of the gastrointestinal changes that occur during aging. These physiologic changes may or may not affect how the patient absorbs a drug. For example, a de-
crease in an elderly patient’s gastric motility can cause a nonsteroidal anti-inflammatory drug to remain in contact with the gastric mucosa for a longer period of time, potentially increasing the risk for ulceration.\textsuperscript{28,29}

Active transport is decreased in the elderly population. Various nutrient drugs such as thiamine, folic acid, calcium, and iron are absorbed via this process.\textsuperscript{30} Use of vitamin supplementation should be a consideration in these patients because vitamin deficiency has been postulated as a medical cause of depression.\textsuperscript{24,29}

Distribution is generally variable in the elderly population. Elderly patients commonly have decreased availability of the plasma protein albumin, which is necessary for the binding of acidic drugs. When plasma albumin is decreased, more active and unbound drug is available to receptors, placing the patient at risk for toxicity.\textsuperscript{31} Factors that may contribute to the decrease in albumin include malnutrition, immobility, and chronic illnesses.\textsuperscript{32}

Conversely, $\alpha_1$-acid glycoprotein (AAG) tends to be increased in the elderly population. AAG is an acute phase reactant protein to which many basic drugs bind. This protein is also increased during acute illnesses and inflammation. The increase in AAG may cause enhanced binding of basic drugs with subsequent decrement in unbound or free fraction of the drug leading to subtherapeutic levels and decreased pharmacologic effect.\textsuperscript{33}

As a person ages, the ratio of lean body mass to fat as well as the total body water content of the person changes, which can affect drug distribution and thus pharmacologic response. A decrease in lean body mass with a subsequent increase in adipose tissue affects the volumes of distribution for hydrophilic as well as lipophilic medications. Between the ages of 20 and 80 years, total body water content is decreased approximately 10\%–15\%. Physical inactivity of the elderly population may also contribute to these changes that occur in body composition.\textsuperscript{34}

Generally, the volumes of distribution as well as the half-lives for hydrophilic medications are decreased in the elderly.\textsuperscript{28} Water-soluble drugs, such as lithium and morphine, are distributed primarily in lean body mass or body water, which is decreased in the elderly population.\textsuperscript{29} Therefore, a lower dose of water-

\begin{table}
\centering
\begin{tabular}{|l|l|l|}
\hline
Pharmacokinetic Process & Physiologic Change & Clinical Significance \\
\hline
Absorption & Altered gastrointestinal motility & Little change in absorption with increasing age \\
& Decreased absorptive surface & \\
& Decreased gastric emptying rate & \\
& Decreased splanchnic blood flow & \\
& Increased gastric pH & \\
& & Increased or decreased unbound concentration of drugs in plasma \\
& & Higher concentration of drugs that distribute into body fluids; altered volume of distribution of some drugs often leads to a prolonged elimination half-life \\
Distribution & Altered protein binding & \\
& Decreased serum albumin & \\
& Increased $\alpha_1$-acid glycoprotein & \\
& Decreased lean body mass & \\
& Decreased total body weight & \\
& Increased adipose tissue & \\
Metabolism & Decreased phase I metabolism & \\
& No change in phase II metabolism & \\
& Decreased hepatic blood flow & \\
& Decreased hepatic mass & \\
& & Decreased hepatic clearance of drugs and metabolites with increased plasma concentrations \\
Elimination & Reduced glomerular filtration rate & \\
& Reduced renal blood flow & \\
& Decreased tubular secretion function & \\
& & Decreased renal clearance of drugs and metabolites with increased plasma concentrations \\
\hline
\end{tabular}
\caption{Physiologic Changes Relevant to Drug Pharmacokinetics in the Elderly}
\end{table}

Adapted from References \textsuperscript{28,29, and 34}. 

\textbf{Table 1. Physiologic Changes Relevant to Drug Pharmacokinetics in the Elderly}
soluble drugs is usually required for these patients to reach therapeutic plasma concentrations. In addition, shorter intervals between administration times may be required due to the decreased half-lives of these water-soluble medications.\textsuperscript{35}

Conversely, lipophilic drugs have increased volumes of distribution as well as increased half-lives in the elderly population due to the accumulation of these agents in adipose tissue. Because of the physiologic alterations in this population, the duration of action and the process of eliminating the drug is delayed, potentially increasing the risk for adverse effects of the drug. For example, sedative-hypnotics and analgesics are given on an intermittent basis to decrease the incidence of adverse effects commonly associated with these agents. Diazepam, a long-acting benzodiazepine, has an almost 2-fold increase in the volume of distribution in elderly patients and a half-life of approximately 90 hours compared to 24 hours in young patients.\textsuperscript{28}

Metabolism in the liver, excretion by the kidneys, or a combination of these processes are the primary mechanisms by which medications are eliminated from the body. Higher plasma drug concentrations with a subsequent increase in pharmacologic response can result due to a decrease in total body clearance that occurs as a person ages, placing the patient at risk for drug toxicity. With increasing age, physiologic changes regarding kidney function have a greater influence on drug elimination compared to physiologic changes in hepatic function.\textsuperscript{29}

Age-related physiological changes that occur in the hepatic system, such as decreased liver mass, hepatic blood flow, and metabolizing activity, contribute to problems with the elimination of medications that are biotransformed in the liver. Other factors such as diet, gender, genetics, smoking, concomitant drugs, and diseases can also affect the process of drug metabolism.\textsuperscript{29} Autopsy studies have shown that between the ages of 20 and 80 years, the size of the liver is decreased approximately 18\textperthousand{}–25\textperthousand{}, which has been associated with a decreased clearance of certain drugs.\textsuperscript{34} In addition, the reduction in hepatic blood flow is the rate-limiting step for medications that are highly metabolized in the liver. As a result, the decline in hepatic blood flow, and thus hepatic clearance of the drug, could increase the plasma drug concentrations to potentially toxic levels.\textsuperscript{29}

Age-related physiologic changes in hepatic metabolizing activity affect the ability of the liver to eliminate certain medications from the body through biotransformation reactions.\textsuperscript{29} These reactions involve both microsomal and nonmicrosomal enzymes and are classified as either phase I or phase II reactions. Phase I reactions are normally reduced in the geriatric patient, while phase II reactions are generally unaffected by normal aging.\textsuperscript{34}

Phase I reactions are associated with the cytochrome P-450 system and involve oxidation, reduction, and hydrolysis, typically producing compounds with pharmacologic activity. The key cytochrome P-450 isoenzymes responsible for the metabolism of certain psychotropic medications include CYP1A2, CYP2D6, CYP3A4, and the CYP2C subfamily.\textsuperscript{36}

Phase II reactions involve glucuronidation, acetylation, and sulfation and usually produce inactive metabolites. For example, chlordiazepoxide, diazepam, and prazepam are benzodiazepines that undergo biotransformation to active metabolites via oxidation, a phase I reaction. All of these agents demonstrate decreased clearance and prolonged elimination half-lives in the elderly population, increasing the risk of excessive sedation and other adverse effects. Alternately, the benzodiazepines lorazepam, oxazepam, and temazepam are metabolized to inactive metabolites by undergoing conjugation, a phase II reaction.\textsuperscript{37} Overall, the cumulative effect of increased volumes of distribution and half-lives in conjunction with decreased hepatic metabolism in the elderly population may dramatically prolong the desired clinical effect of numerous medications.

Renal function progressively declines with age and provides the most consistent reflection of aging on pharmacokinetic variables.\textsuperscript{34,35} Effects such as reduced renal blood flow, reduced
glomerular filtration rate (GFR), lack of glomeruli in the renal cortex, and diminished tubular secretion lead to renal impairment in the elderly population. Generally, renal blood flow declines 1.9% every year. The GFR may decline as much as 50% as age increases, likely resulting in lesser elimination of drugs that are partially or completely cleared by the kidneys. Drug elimination is associated with creatinine clearance. On average, the creatinine clearance of an individual declines by 50% from the ages of 25 to 85 years. Common methods of estimating creatinine clearance, such as the ubiquitous Cockcroft and Gault formula, should be used with a certain degree of caution because some studies have suggested that the formula may not be accurate for residents of nursing homes.

Decreased renal elimination may lead to prolonged half-lives of medications excreted by the kidneys, resulting in increased plasma concentrations. This is particularly important for medications with narrow therapeutic indices, as clinically significant adverse effects may occur in elderly patients if dosages are not adjusted accordingly. In addition, elimination of hydroxy metabolites of tricyclic antidepressants, which are potentially cardiotoxic to elderly patients, is dependent on renal function. Since renal function usually declines with age, accumulation of cardiotoxic metabolites may occur and can potentially lead to impaired cardiac conduction.

**TREATMENT**

The overall goal of any antidepressant treatment modality is to improve and maximize quality of life, to maintain independent living skills in a community setting, and finally to avoid or delay placement in a long-term care facility or nursing home. In most treatment facilities, the older depressed individual is most likely to be evaluated and subsequently treated by a primary care practitioner. Psychiatric referral to a mental health specialist should be made in treatment refractory patients or in high-risk situations such as suicidality or in individuals with complex comorbidities. Baseline evaluations should include a complete physical exam including laboratory studies. Clinicians should also routinely make use of well-validated rating scales such as the patient-rated Geriatric Depression Scale or the clinician-administered Hamilton Depression Rating Scale. The use of these scales improves diagnostic reliability and can give the clinician a concrete mechanism to evaluate symptom progression, symptom severity, and antidepressant efficacy. A complete drug history, including past antidepressant treatment successes and failures, should be recorded at baseline.

Individualization of overall antidepressant treatment is key to the successful treatment of the elderly depressed patient. Symptom severity, disease comorbidity, economic means, expected tolerance to adverse effects, concurrent drug therapies, and patient attitude must be taken into consideration when developing an initial treatment plan. Psychotherapies may be used as the primary therapy in mild depression or may be combined with antidepressants in more moderate or severe depression. Severe or treatment-resistant depression may respond to a course of electroconvulsive therapy (ECT). Clinicians that are presented with a clinical case involving a possible disease-induced depressive episode should generally treat both the depression and the underlying disease for maximal efficacy. Concurrent medications that are known to worsen depression should be evaluated for possible substitution.

Psychotherapies for geriatric patients, such as group therapy, family therapy, and cognitive therapy, can aid in understanding and adapta-
tion to the inevitabilities of older age. These nonpharmacological therapies can improve self-esteem, reduce helplessness and anger, and can improve quality of life. Common issues for the geriatric patient involve grief, family and peer losses, assumption of new roles, and acceptance of mortality. Group therapy is especially effective in that it can provide an opportunity for mutual support as well as provide a mechanism for new friendships at a time when many long-term friends may have died. Family therapy helps to increase familial understanding of the changes that an elderly person is undergoing. Involving family can reduce resentment, prevent elder abuse, and can provide the depressed individual with a sense of belonging and support. Cognitive therapy can minimize self-induced prejudices about growing older. Cognitive therapy can correct distortions in thinking, especially as relates to new skill acquisition, maintenance of sexual activity, learning, and helping others.

ECT has been shown to be a safe and effective treatment for elderly depression, especially in the context of symptom severity, treatment resistance, or the presence of psychosis. ECT has been shown to be a safe and effective treatment for elderly depression, especially in the context of symptom severity, treatment resistance, or the presence of psychosis. In fact, elderly individuals make up over one-half of patients who receive ECT in the United States. Although most studies of ECT have included only young-old patients, a more recent study has concluded that ECT is safe and effective in the old-old patient. The overall conclusion of this most recent study was that despite a higher medical comorbidity and worsened cognitive functioning, ECT is tolerated as well as in younger patients and acute response was similar or better than seen in younger patients.

Antidepressant selection, as in younger patients, should be based on past history of response, avoidance of adverse effects, presence of comorbidities, concurrent medications, and any known age-related physiological change that would impact pharmacodynamic or pharmacokinetic functioning. The lowest effective dose of any antidepressant should be used to minimize toxicity and enhance patient acceptance and compliance. The time-honored maxim to “start low and go slow” has particular significance and application in the elderly. Table 2 describes the usual dosage recommendations of commonly used antidepressants in elderly depression.

**PHARMACOTHERAPY**

**Selective Serotonin Reuptake Inhibitors**

The selective serotonin reuptake inhibitors (SSRIs) are as efficacious as TCAs and have become the preferred medications for the treatment of depression in most elderly patients due to easier dosing schedules and more tolerable adverse effects. Although all SSRIs appear to be effective for late-life depression, only paroxetine has been studied in patients older than 80 years of age. The primary difference between the SSRIs involves pharmacokinetic parameters. The SSRIs are highly protein bound and undergo extensive metabolism. Paroxetine, sertraline, and fluvoxamine have relatively shorter half-lives compared to fluoxetine and citalopram. Norfluoxetine, the active metabolite of fluoxetine, has a 7 to 9 day half-life, possibly leading to accumulation in

| Table 2. Dosage Recommendations of Selected Antidepressants in the Elderly |
|-----------------------------|-----------------|-----------------|
| **Medication**              | **Adult: Age < 65 (mg/day)** | **Geriatric: Age ≥ 65 (mg/day)** |
| Amitriptyline              | 75–300          | 25–150          |
| Bupropion                  | 225–450         | 50–100          |
| Citalopram                 | 20–40           | 20              |
| Desipramine\(^1\)          | 75–300          | 10–100          |
| Doxepin                    | 75–300          | 10–75           |
| Fluoxetine                 | 20–80           | 10–40           |
| Fluvoxamine                | 50–300          | N/A             |
| Imipramine                 | 75–300          | 10–150          |
| Mirtazapine                | 15–45           | N/A             |
| Nefazodone                 | 300–600         | N/A             |
| Nortriptyline\(^2\)        | 75–300          | 10–75           |
| Paroxetine\(^2\)           | 20–50           | 10–30           |
| Sertraline\(^2\)           | 75–200          | 25–200          |
| Trazodone                  | 150–600         | 25–150          |
| Venlafaxine                | 75–375          | N/A             |

\(^1\)Not recommended for use in geriatric patients.

\(^2\)Preferred antidepressant in geriatric patients.

Adapted from References 29 and 57.
the adipose tissue of elderly patients. Clinically, agents with longer half-lives have the advantage of increased compliance and stable blood concentrations if doses are missed, while agents with shorter half-lives possess the advantage of increased dosing flexibility. Drug interactions are also a concern due to hepatic metabolizing enzymes that are shared between SSRIs and other medications that are frequently prescribed in this population.39 Compared to the TCAs, the SSRIs reportedly cause more gastrointestinal (GI) adverse effects such as nausea and vomiting, especially during the first few weeks of therapy. To help alleviate or lessen GI irritation, the patient should consume food 20 to 30 minutes before taking these medications.48 In addition, the elderly patient should also be monitored for weight loss, especially in the low-weight elderly. The SSRIs, especially fluoxetine, may cause agitation, anxiety, and/or insomnia in elderly patients. Decreasing the dose or switching to a less stimulating antidepressant may be helpful in these patients.48,49

Another adverse effect associated with the SSRIs is drug-induced parkinsonism. This syndrome is characterized by dystonias, akathisia, and potential exacerbation of symptoms in elderly patients suffering from idiopathic Parkinson’s disease.50,51 In addition, a rare adverse effect associated with both the TCAs and SSRIs is the syndrome of inappropriate antidiurectic hormone secretion (SIADH). Although both SIADH and parkinsonism have been primarily reported with fluoxetine, data regarding these adverse effects are limited.52,53

Recommended starting doses for the SSRIs in the elderly population are generally between one-third and one-half of the usual dose for young and middle-aged adults. Doses of SSRIs are usually administered in the morning due to the stimulating effects, but can be given at bedtime if the patient complains of sedation.48

**Other Newer Antidepressants**

The other newer antidepressants, bupropion, trazodone, nefazodone, venlafaxine, and mirtazapine, may also play a role for elderly patients suffering from depression. Compared to the TCAs and the SSRIs, these agents have been studied to a lesser extent in the elderly population. Although there are fewer studies in these patients, clinical experience indicates that these antidepressants are effective in the elderly. Similar to other antidepressants, these agents should be initiated with lower doses and slowly titrated to effect in elderly patients.

Bupropion is considered to be a favorable antidepressant in many elderly patients due to its minimal anticholinergic, sedative, orthostatic, and cardiovascular adverse profile. Bupropion is believed to inhibit the reuptake of dopamine, norepinephrine, and serotonin. The aspect of dopamine reuptake inhibition may be especially useful in patients suffering from depression who also have been diagnosed with Parkinson’s disease. Common adverse effects include nausea, vomiting, agitation, and insomnia.48 Because this medication tends to be activating for most patients, administration at bedtime should be avoided. Another adverse effect that limits dosing is the increased risk of seizure activity at single doses greater than 150 mg or total daily doses greater than 450 mg. Bupropion should be avoided in patients with seizures.39,48 Elderly patients should be initiated with 75 mg twice daily with at least 6 to 8 hours between each dose.48 The availability of a sustained-release (SR) formulation offers another option for elderly which may improve compliance. Approximately 6000 patients participated in clinical trials with the SR formulation in which 275 patients were 65 years and over and 47 were 75 years and older. There were no overall differences in the clinical effectiveness or safety profile between younger and older patients. With the SR formulation, elderly patients should be initiated with 150 mg SR daily, preferably as a morning dose.54

Trazodone is believed to inhibit the reuptake of serotonin as well as antagonize the serotonin-2 postsynaptic receptor, which may contribute to anti-anxiety effects reported with this medication. Trazodone also antagonizes alpha-1-adrenergic receptors, resulting in significant
orthostatic hypotension that commonly occurs 1 to 2 hours after administration. This adverse effect greatly limits its usefulness as a clinically effective antidepressant, especially in elderly patients. Trazodone also inhibits alpha-2-adrenergic receptors, which has been reported to rarely induce priapism in patients. Although trazodone lacks significant anticholinergic adverse effects, the agent produces significant sedation in patients. For this reason, the most common use of trazodone in the geriatric population is as a sedative-hypnotic. However, for elderly patients who have been resistant to other antidepressant therapy, trazodone may be considered as an alternative medication.

Nefazodone is another atypical antidepressant that has been used in elderly patients. Like trazodone, this serotonergic agent is believed to inhibit the reuptake of serotonin as well as antagonize serotonin-2 postsynaptic receptors. Adverse effects frequently experienced with this medication include sedation, headache, and orthostasis. This antidepressant has minimal to no anticholinergic effects, cardiac conduction abnormalities, or seizure risk and has been found to be safer than TCAs in overdose. Nefazodone is metabolized to 3 active metabolites that have relatively shorter half-lives and therefore requires twice daily dosing. Due to sedation and orthostasis that may occur with this medication, doses as low as 50 mg twice daily are recommended for initiating drug therapy in elderly patients. Additionally, nefazodone inhibits the CYP3A4 enzyme which is responsible for metabolizing many other medications. Because elderly patients are commonly prescribed multiple medications, it is important to monitor the patient's medication profile for potential drug interactions with nefazodone.

Venlafaxine is generally used as a second-line agent in elderly patients who have not responded to other antidepressant therapy. This antidepressant resembles the pharmacologic profile of the TCAs in that it selectively inhibits the reuptake of both norepinephrine and serotonin from the synaptic cleft. However, venlafaxine lacks the anticholinergic effects that are commonly associated with the TCAs. Adverse effects associated with venlafaxine include nausea, headache, insomnia, confusion, and a possible elevation in blood pressure. The adverse effects of venlafaxine emphasize the need for caution with its use in the elderly population, especially those with brittle or severe hypertension. This agent is metabolized to an active metabolite by the cytochrome P-450 system and is also excreted through the kidneys. Therefore, dosage adjustments may be required in elderly patients with renal impairment.

Mirtazapine is a relatively new antidepressant that antagonizes alpha-2 receptors and is postulated to cause an increase in noradrenergic and serotonergic activity. This agent is also believed to antagonize 5-HT2 and 5-HT3 receptors. Adverse effects associated with mirtazapine include sedation, orthostasis, increased appetite, weight gain, and increases in triglycerides and total cholesterol. Because mirtazapine is substantially excreted by the kidney (75%), dosages must be adjusted in patients with decreased renal function. A majority of elderly patients have impaired renal function and consequently require a lower dose, especially on initiation of therapy. Due to the risk of oversedation and orthostasis with mirtazapine, this antidepressant should be reserved as second-line therapy in the elderly population.

TCAs

TCAs are effective medications for elderly patients diagnosed with major depression but are more frequently used in lower doses for chronic pain syndromes. The TCA adverse effect profile of anticholinergic effects (dry mouth, blurred vision, constipation, confusion), inhibition of histamine-1 receptor activity (sedation), inhibition of alpha-1-adrenergic activity (orthostatic hypotension), and prolongation of cardiac repolarization (responsible for widening of the QT interval) reduce their utility in the elderly. The cardiac effects can make TCAs contraindicated in many elderly patients.
patients. The secondary amines (desipramine and nortriptyline) are the preferred TCAs for elderly patients due to decreased adverse effects and the availability of serum concentration monitoring. However, significant adverse effects have been noted in patients who were within the therapeutic range for the medications. For this reason, geriatric patients should also be monitored for signs and symptoms of toxicity, whether mild (blurred vision, urinary retention, and confusion) or severe (arrhythmias and respiratory depression).

Elderly patients with cardiovascular disease, benign prostatic hypertrophy, urinary retention, narrow-angle glaucoma, or a history of seizures should be closely supervised while using TCAs. Anticholinergic effects such as dry mouth and constipation may cause severe problems within the gastrointestinal system. Central nervous system anticholinergic effects of these agents are more pronounced in elderly patients and may cause difficulties with memory and attention, potentially escalating to severe cognitive impairment over time. TCAs should be dosed at bedtime to decrease the incidence of falls, which can be serious or possibly fatal in these patients. Caution is also advised in elderly patients with suicidal ideation, given that an accidental or purposeful overdose of as little as a 2-week supply of TCAs can prove to be lethal.

Before initiating TCA therapy in an elderly patient, the clinician should obtain a complete physical exam including an electrocardiogram (ECG). Use of the ECG aids the clinician in monitoring the patient for potential cardiotoxic effects of the TCAs. Starting doses should be especially low (e.g., amitriptyline equivalents 10–25 mg qd), and titrated upward to a dose that elicits the therapeutic response with the least amount of adverse effects. See Table 2 for the usual dosage recommendations of the TCAs and other commonly used antidepressants in elderly depression.

**Monoamine Oxidase Inhibitors**

The monoamine oxidase inhibitors (MAOIs), phenelzine and tranylcypromine, because of their adverse effects and drug-drug and drug-food interactions, have not been well studied in the geriatric population. These medications are not considered first-line agents used for major depression. However, the MAOIs may be effective for elderly patients suffering from atypical depression that is characterized by dysphoric mood accompanied by increases in vegetative symptoms such as sleep, appetite, and libido. MAOIs should only be prescribed to responsible, compliant elderly patients or to elderly patients whose medications are closely supervised.

**CONCLUSION**

Depression in the elderly is underdiagnosed, undertreated, and associated with poor outcomes. Older depressed individuals are at risk for cardiovascular disease, poor quality of life, increased risk of suicide, and worsened prognosis of medical comorbidities. Treatment options are numerous, effective, and now more tolerable than in the past. The SSRIs are currently recognized as the preferred pharmacotherapy due to their improved adverse effect profile, ease of dosing, and documented efficacy across all geriatric age groups. Other treatment options, in the case of treatment failure or treatment intolerance, include bupropion, venlafaxine, and the secondary TCAs, nortriptyline and desipramine. Failure to recognize and treat depression in the elderly has economic, psychosocial, and ethical consequences. As the “baby boomer” generation ages, increased focus and attention on depression in the older patient will become even more of a priority.
REFERENCES


JOURNAL OF PHARMACY PRACTICE, Volume 14, Number 6, December 2001
Several depressive disorders are unique to women, affecting them at various points in their life cycle. These disorders include premenstrual dysphoric disorder (PMDD), pregnancy-associated depressive disorders, and perimenopausal affective disorders. Recently, the importance of the relationship between depression and the reproductive cycle has been highlighted due to the approval of medications to treat (PMDD). The role of gender difference in the prevalence of depressive disorders has long been recognized. This article will examine whether there are differences between men and women in the clinical presentation of depression, including differences in symptom manifestation, course of illness, comorbidities, and treatment. Systematic evaluation of the role of hormonal and neuroendocrine factors may lead to more appropriate treatment of depressive disorders in women.

KEY WORDS: depression, women, life span, hormones, pregnancy.

INTRODUCTION

For many years, issues unique to depression in women have been ignored. Epidemiological studies have long suggested that there is a higher prevalence of depression in women as compared to men. The National Comorbidity Survey showed that women are approximately 1.7 times more likely than men to report a major depressive episode during their lifetime.1 Other differences may exist with respect to presentation, comorbidities, and treatments. This paper will examine whether there are differences in the clinical presentation of depression, including differences in symptom manifestation, course of illness, comorbidities, and treatment between men and women. Other issues include whether effective clinical practice should treat men and women identically and what interactions exist between depression and the reproductive cycle.

PATHOPHYSIOLOGY

There has been significant research to investigate the potential reasons for the difference in prevalence of depression in men and women. Three hypotheses have been postulated to explain the greater prevalence of depression in women: artifact theory, psychosocial theory, and the biological theory.2–4 The artifact theory attributes the gap to gender differences in help-seeking behavior and symptom reporting, as well as bias in diagnosis. The psychosocial explanation points out the effects of gender-specific socialization, role-strain, life stress, lower social status, victimization, and maladaptive coping styles.3 More recently, greater consideration is being given to the biological theories that could explain the gender difference in the prevalence of depression. Biological theories have focused on brain structure and
function differences as well as neurotransmitter, neuroendocrine, and circadian system differences between men and women.²

PRESENTATION

Symptoms and Severity

Some studies have suggested differences in symptom presentation, such as more findings of increased weight and appetite in unipolar major depression in women as compared to men.³,⁵,⁶ Studies have also suggested that women may have more anxiety and somatic symptoms, whereas men may report more weight loss.²,⁶ Depressed women may also be more likely to report a greater number of symptoms than depressed men. Most studies have not consistently shown that there is a gender difference in severity of symptoms of major depression (MD).²,⁵,⁶ Some investigators have reported that depression in women may be more severe and associated with an increase in functional impairment, but this view is not yet widely accepted.⁷ Further research is required to explore these issues with regard to clinical application.

Women are more likely to have atypical depression.

Age at Onset

There is some evidence to indicate that there is an earlier age of onset of MD in women, with men becoming symptomatic in their 20s and women in mid-adolescence.⁶ The National Comorbidity Survey indicates the age of onset may be as early as age 10 in females. This is significant due to speculation that the sex difference in depression is triggered by puberty.¹

Chronicity and Recurrence

Keeping in mind that there is clear evidence that women are more likely to become depressed, a related question is whether women are more likely than men to stay depressed. Some evidence suggests that women may have a more chronic and recurrent course of depression than men. Simultaneously, other studies have shown no sex differences in recurrence or chronicity.²

Comorbidity

Depressed patients with comorbid disorders have a less successful treatment outcome as compared with those who have uncomplicated depression.³ Depressed women have been found to have higher rates of comorbidity than depressed men, making treatment more difficult. Women appear to be especially more prone to medical conditions such as thyroid disorders, rheumatologic disorders, and migraine headaches.³ Anxiety disorders, particularly panic disorder and phobic disorders, are especially prevalent comorbid disorders in depressed women.³,⁶

PHARMACOKINETICS/PHARMACODYNAMICS

There is a paucity of data regarding gender differences in pharmacokinetics and pharmacodynamics in general. Recently, a number of studies have investigated gender differences in pharmacokinetics and pharmacodynamics of psychotropic medications.²,³,¹⁰,¹¹ Alterations in pharmacokinetics may include disparities in absorption, distribution, metabolism, and elimination. Women may secrete less gastric acid
than men and may also have a slower gastrointestinal transit time, particularly at times when progesterone levels are increased. With regard to distribution, it is known that the ratio of body fat to muscle is higher in women, and this increased proportion of body fat can increase the volume of distribution. There is conflicting evidence regarding gender differences in metabolism of antidepressant drugs, specifically when examining variations in effects on the cytochrome P450 (CYP) enzymes. There have been reports of lower clearances of tricyclic antidepressants (TCAs), such as amitriptyline, imipramine, and clomipramine, resulting in higher plasma levels of these antidepressants. Still, more trials are needed to evaluate gender differences in metabolism of TCAs. Clinical pharmacokinetics of selective serotonin reuptake inhibitors (SSRIs) have been extensively evaluated, but studies thus far have not shown sex to be a significant factor influencing their disposition.

Women may be more prone to adverse effects and drug toxicity as compared to men.

Clinical implications of the pharmacokinetic differences are that women may be more prone to adverse effects and drug toxicity as compared to men, due to altered plasma levels and longer half-lives of drugs.

Very few studies have looked at gender differences in treatment response to antidepressant medications. Some studies have suggested that women respond more poorly to TCAs than SSRIs as compared to men. It has also been suggested that women may respond more slowly to antidepressant medications.

HORMONAL INFLUENCES

The effects of exogenous as well as endogenous hormones on mood regulation is an area of significant interest among researchers. The effect of exogenous hormones on depression and antidepressants in women can be seen in the observations that women taking oral contraceptives had higher imipramine levels. It has often been speculated that endogenous hormones affect the disposition of antidepressants as well as play a pertinent role in depressive disorders in women. Studies have shown menstrual cycle variations in drug levels during the premenstrual period and alterations in dosage requirements during pregnancy and the puerperium.

The importance of the relationship between depression and the reproductive cycle is heightened because of the approval of medications to treat premenstrual dysphoric disorder (PMDD) and the data suggesting a role of estrogen as an antidepressant. It is no surprise that mood and behavior may be correlated with gonadal hormone levels. Estrogen has been evaluated as monotherapy and adjunctive therapy with antidepressant medications for its use in postmenopausal women and women with postpartum depression and refractory depression. The ability of estrogen to modulate serotonergic function has led to increased speculation about the role that sex hormones play in the mechanisms associated with depression and its treatment. Estrogen increases acetylcholine synthesis by increasing levels of choline acetylcholinesterase and helps to maintain dendritic spine density in the hippocampus. Estrogen is thought to enhance serotonergic transmission by decreasing monoamine oxidase levels, increasing free tryptophan availability to the brain by displacing tryptophan from albumin, and enhancing serotonin transport. The enhanced serotonin neurotransmission with estrogen could potentially help improve mood in depressed women. Involvement of the hypothalamic-pituitary-thyroid axis is often postulated as a contributing factor in depression in women. Simultaneous use of thyroid supplementation with an antidepressant is not recommended unless the patient has a past history of a major depressive episode with normal thyroid function or, in the judgment of the clinician, the
patient’s depressive symptoms are quite severe when compared with the thyroid deficiency. Augmentation with thyroid hormone may result in nervousness and insomnia. Estrogen can induce or exacerbate depression, especially when administered at times that will oppose circadian rhythms. The progesterone component of sequential hormonal replacement therapies has also been noted to cause depression. The role of the reproductive system and neuroendocrine differences in depression and its treatment may be evaluated by examining the various types of depression during the various phases of reproductive cycle in women.

**Diagnostic Differences**

There are several depressive disorders that are unique to women, affecting women at various stages of life, including PMDD, pregnancy-associated depressive disorders, and perimenopausal affective disorders. Systematic evaluation of this issue may lead to more appropriate treatment of depressive disorders in women.

**PMDD**

PMDD is a more severe form of what has previously been described as premenstrual syndrome (PMS) that is characterized predominantly by mood symptoms and results in significant impairment of social and occupational functioning. The diagnostic criteria for PMDD as outlined in the *Diagnostic and Statistical Manual of Mental Disorders*, (4th ed.) (DSM-IV), requires a minimum of 5 symptoms, 1 of which must be a mood symptom such as depressed mood, feeling anxious/tense, marked lability, and/or irritability. These symptoms must regularly occur during the last week of the luteal phase and begin to remit within a few days after the onset of menses. The symptoms of PMDD must markedly interfere with work, school, or usual social activities and relationships with others. Other symptoms may include decreased interest, difficulty concentrating, lethargy, and marked changes in appetite and/or sleep patterns, as well as other physical symptoms.

PMDD was initially described as late luteal phase dysphoric disorder in the DSM-III-R as a condition in need of further study. PMDD is now described in the section of the DSM-IV under “depressive disorder not otherwise specified.” This is clear evidence of the relationship that this disorder has to other depressive disorders. Many of the criteria for PMDD overlap with the symptoms of major depression including depressed mood, affective lability, decreased interest, difficulty concentrating, fatigue, changes in appetite, and hypersomnia or insomnia.

Approximately 20%–80% of menstruating women report mild to moderate mood or somatic symptoms related to the late luteal phase of the menstrual cycle. The prevalence rates for PMDD are much lower at an estimated 2%–10%. The low rate of PMDD in comparison to PMS is thought to be due to the inclusion of severity criterion specifying that the disorder has interfered significantly with normal function by causing severe disruption of work or relationships. The requirement of confirmation of symptoms and impairment by prospective daily ratings during at least 2 consecutive symptomatic cycles may also result in a lower rate of PMDD as compared to reports of premenstrual symptoms.

The course of PMDD is thought to become more severe, extend in duration, and become more refractory to treatment with time, similar to the course of a recurrent major mood disorder. Onset of PMDD typically occurs during the teens to late 20s, while symptoms usually peak in the 30s and early 40s. There is evidence that untreated PMDD may progress to a major depressive disorder. Studies have shown that women with PMDD are at a higher risk for developing a major depressive episode as compared to women without premenstrual complaints. It has also been suggested that between 30% and 60% of women with major depressive disorder experience a worsening of symptoms premenstrually.
Variations in prevalence and manifestation findings for PMDD may be due to lack of consistency in application of diagnostic criteria and measurement techniques. Validated and standardized instruments useful in the diagnosis and assessment of PMDD include the Structured Clinical Interview for DSM-IV Depressive Disorders and Structured Interview Guide for the Hamilton Depression Rating Scale. Scales designed specifically for assessment of PMDD symptoms that should correspond to DSM-IV criteria include the Menstrual Distress Questionnaire, the Premenstrual Affective Form, and Calendar of Premenstrual Experiences (COPE). Symptoms and severe impairment in occupational and relationship functioning must be confirmed by prospective daily ratings during at least 2 consecutive symptomatic cycles. Other components of a complete evaluation should include a physical and gynecological examination as well as further biological tests including thyroid function tests, chemistry panel, electrolytes, and luteal progesterone level or urine ovulation tests for the midcycle luteinizing hormone surge to document ovulation.

Although it is clear that PMDD is closely related to other depressive disorders, the etiology of PMDD has not been established. Several theories have been proposed regarding the etiology of PMDD, including changes in reproductive hormone levels, an increase in prostaglandins, abnormalities of the hypothalamic-pituitary-adrenal function, decrease in β-endorphin levels, and decrease in gamma-aminobutyric acid levels during the luteal phase in women with dysphoric premenstrual symptoms. Research has shown that the symptoms of PMS or PMDD are not directly attributable to the changes in hormone levels during the late luteal phase of the menstrual cycle. Therefore, it is believed that premenstrual symptoms may be an abnormal reaction to the usual fluctuations in reproductive hormones during the menstrual cycle. A large portion of the biological investigations in PMDD has involved the role of the neurotransmitter system that has been most heavily implicated in depressive disorders, serotonin, or 5-hydroxytryptamine (5-HT). The serotonergic system has been evaluated in a variety of ways to determine its role in the pathophysiology of PMS and PMDD, including measurements of serotonin in whole blood, platelet 5-HT uptake, and neuroendocrine challenge. It has also been noted that depletion of the serotonin precursor tryptophan is significantly more likely to provoke premenstrual symptoms in PMDD patients as compared with asymptomatic women.

Treatment

A variety of treatments has been investigated for use in PMDD. Alleviation of symptoms has been seen with gonadotropin-releasing hormone agonists in combination with hormone replacement. Alprazolam has received considerable attention as a treatment for PMDD symptoms. Alprazolam was shown to be significantly superior to placebo and also more efficacious than progesterone. Unfortunately, its use has been limited due to concerns of abuse and dependence potential as well as significant sedative effects. The most promising results have been seen with serotonergic agents including the SSRIs, buspirone, and clomipramine. Trials of serotonergic antidepressants have shown significant drug improvement ranging from 52%–69% in treatment of PMS/PMDD.

Fluoxetine has been most extensively studied and was recently approved by the Food and Drug Administration as safe and effective treatment for women with PMDD. Fluoxetine has been studied at daily doses of 20 mg and 60 mg per day administered continuously throughout the menstrual cycle, with 20 mg daily appearing beneficial for most patients. Benefits of
fluoxetine have been seen during the first month of therapy, which is noticeably more rapid than the antidepressant response. This may indicate that fluoxetine’s mechanism of action in PMDD is different than the mechanism of action in depression.\textsuperscript{15,18} Data for efficacy from controlled trials also exist for sertraline, paroxetine, and clomipramine.\textsuperscript{15–20}

Several studies have compared the SSRIs with nonserotonergic antidepressant medications for the treatment of PMDD.\textsuperscript{16,21–23} The results of these studies suggest that SSRIs are superior to other nonserotonergic antidepressant agents and further substantiate the theory that serotonin plays an essential role in mediating premenstrual symptoms.

Recent studies have examined intermittent dosing strategies for PMDD. Young and colleagues found that sertraline given only during the luteal phase was significantly more effective than placebo in reducing both behavioral and physical symptoms as assessed by the COPE.\textsuperscript{20}

Further research is needed to determine the long-term efficacy of SSRI use in the treatment of PMDD. There is some evidence that response to fluoxetine may be maintained for up to 18 months.\textsuperscript{15,18}

**DEPRESSION IN PREGNANCY**

Pregnancy and childbirth represent periods of unparalleled neuroendocrine and psychosocial changes in a woman’s life. Therefore, it is not surprising that women of childbearing age are especially susceptible to affective disorders.\textsuperscript{24} Although it has long been believed that pregnancy is a time of emotional well-being and may provide some protective effect against mental disorders, there is little data to support this clinical belief.\textsuperscript{24,25} During pregnancy, up to 70\% of women may experience depressive symptoms, while 10\%–16\% would meet DSM-IV criteria for major depression.\textsuperscript{24} These rates are consistent with those seen in the general population and would suggest that pregnancy does not confer any greater risk of depression. However, these rates may not be indicative of the true prevalence of depression during pregnancy due to various limitations in assessment and diagnosis of depression during pregnancy. There is considerable overlap of symptoms between major depression and the normal sequelae of pregnancy. Depressive symptoms, such as changes in appetite, body weight, and sleep, are more likely to be attributed to the pregnancy than to a depressive episode. Further complicating the assessment of depression during pregnancy is the failure to assess for medical disorders such as anemia, gestational diabetes, and thyroid dysfunction that could potentially contribute to depressive symptoms.\textsuperscript{24} Appropriate treatment of major depression must start with proper identification and assessment.

Several risk factors for depression during pregnancy have been identified. Risk factors for depression in pregnancy include prior history of depression, family history of depression, marital discord, recent stressful life events, limited social support, and ambivalence about pregnancy or unwanted pregnancy. One of the most important risk factors to consider is the prior history of depression. Data on recurrence and relapse rates upon discontinuation of antidepressant therapy are limited, but recurrence rates have been estimated to be as high as 50\% within 6 months following discontinuation of antidepressant treatment.\textsuperscript{26} Therefore, there is a high probability that women who discontinue antidepressant treatment close to conception will experience a recurrence of depression during the course of the pregnancy that will require treatment. It is important to consider the risks and benefits of treatment to both mother and fetus. In moderate to severe major depression, it is commonly held that the benefits of treatment with antidepressant agents far outweigh the risks. Untreated depression in the mother may lead to increased risk of maternal suicide, inadequate prenatal care, poor nutrition, obstetric complications ( prematurity and low birth weight), and postpartum depression.\textsuperscript{26,27}

Decisions about pharmacological treatment of depression are extremely challenging. For
understandable ethical reasons, there is a lack of data and research regarding the effects of pharmacological agents in pregnancy. Toxicities due to medication use during pregnancy may be divided into three main categories: teratogenicity (organ or congenital malformation), neonatal toxicity including perinatal syndromes and withdrawal symptomatology, and long-term neurobehavioral and developmental sequelae (behavioral teratogenicity). Treatment of depression during pregnancy requires multiple considerations including past response to medication and risk-benefit assessment of pharmacological therapy.

The majority of data regarding drug use during pregnancy has been accumulated from cohort-controlled or case-controlled studies, anecdotal reports, and retrospective evaluations due to the lack of randomized, placebo-controlled studies for ethical reasons. The most data for antidepressant use in pregnancy is found for TCAs and SSRIs. Ericson and colleagues recently investigated delivery outcomes after the use of antidepressants in early pregnancy. Antidepressant use in 969 women (531 used only SSRIs [375 citalopram exposures], 423 used only other antidepressants, and 15 used both) was recorded and compared with all births in the population for the Swedish Medical Birth Registry. The outcome variables in the study included multiple births, short gestational duration (<37 completed weeks), low birth weight in single births, perinatal mortality, and congenital malformations. Findings of the study were that women using antidepressants had a tendency to deliver preterm more often than other women, but this could be due to confounding factors (smoking, disease process) rather than the effects of the drugs. There was an increased rate of low birth weight infants, but this may have also been attributable to confounding variables. Ericson and colleagues found that the effect on birth weight was less pronounced and disappeared after considering maternal age, parity, and smoking habits. The observation of a lower than expected rate of multiple births in women who used SSRIs but not in women using other antidepressants requires further investigation. No evidence of teratogenic effect of either SSRIs or other antidepressants was found. These findings are consistent with those seen in most studies to date. In prospective, controlled studies of SSRI exposure during pregnancy published since 1993, only one, which evaluated fluoxetine exposure during pregnancy, reported an increased risk of minor anomalies, while infants exposed during the third trimester had higher rates of premature delivery, respiratory difficulty, cyanosis, jitteriness, and low birth weight. Methodological flaws in this study limit the usefulness of the information. The finding of perinatal distress was also inconsistent with other studies that noted no perinatal distress in infants exposed to fluoxetine in late pregnancy.

Available reports and data indicate that exposure to SSRIs as well as TCAs during pregnancy does not result in increased risks to the mother or infant. Pastuszak and colleagues compared pregnancy outcomes of 128 women exposed to fluoxetine to 2 matched groups of women exposed to either nonteratogens (n=128) or TCAs (n=74) during the first trimester of pregnancy. Comparable rates of major malformation were found between the 3 groups and did not exceed the expected rate in the general population. Rate of miscarriages was comparable between the fluoxetine-treated group and TCA-treated group but was higher than the nonteratogen control group (13.5% and 12.2% vs. 6.8%). Kulin and associates reported on 267 women exposed to SSRIs [147 on sertraline, 97 used paroxetine, and 26 used fluvoxamine (3 women used a combination of two)] compared to 267 controls. Primary outcome measures were rates of major congenital malformations. Results of the
A study showed that exposure to SSRIs was not associated with increased risks for major malformations or higher rates of miscarriage, stillbirth, or prematurity. Mean birth weights and gestational ages were similar for SSRI users as compared to controls. Outcomes of 796 pregnancies identified prospectively with confirmed first-trimester exposure to fluoxetine contained in the manufacturer’s pregnancy registry were evaluated and compared with historic reports of newborn surveys. The investigators concluded that maternal fluoxetine use during the first trimester of pregnancy resulted in no differences in rates of occurrence of fetal malformations. A meta-analysis of 414 cases of first-trimester exposure to TCAs showed no significant association between fetal exposure to TCAs and high rates of congenital malformations.

TCA withdrawal syndromes during the perinatal period, characterized by symptoms of jitteriness, irritability, and convulsions, have been reported in children exposed to TCAs during the labor and delivery period. Symptoms of functional bowel obstruction and urinary retention that are thought to be attributable to anticholinergic effects of TCAs have also been reported.

Studies and data reporting long-term effects of any antidepressants are severely lacking. One study reported on neurodevelopment of children exposed in utero to antidepressant drugs. This study examined the global IQ scores, language development, and behavioral development of children of mothers exposed in utero to TCA, fluoxetine, or no antidepressant medication. Global IQ scores and language development were assessed between 16 and 86 months of age postnataally. The researchers found that in utero exposure to either TCA drugs or fluoxetine does not affect global IQ, language development, or behavioral development in preschool children. Another study reporting potential long-term behavioral changes in children exposed in utero to TCA found that children followed up to 3 years after birth had normal motor skills and behavioral development.

There are limited data regarding the use of newer antidepressant agents including bupropion, mirtazapine, nefazodone, trazodone, and venlafaxine. Therefore, these agents should be used with caution during pregnancy. The clinician should carefully review the benefit-to-risk ratio with these newer antidepressant agents.

An additional factor that may result in mood changes across pregnancy in women treated with antidepressant medication is the change in plasma drug levels of antidepressants during pregnancy. It has been noted that increased volume of distribution, increased hepatic enzyme activity, and/or increased renal clearance rates during pregnancy may result in decreased antidepressant levels. Therefore, clinicians should carefully observe their pregnant patients for depressive symptoms secondary to decreased serum levels of antidepressant medications. Serum levels of antidepressants, particularly tricyclic agents, may be monitored in pregnant women and dose adjustments made accordingly.

In conclusion, pharmacological intervention is appropriate for women who develop moderate to severe depression during pregnancy. Patients taking antidepressants when they become pregnant should have treatment continued if they previously attempted to discontinue antidepressant therapy during or prior to pregnancy with resultant relapse. Patients with a single, uncomplicated episode in remission may be able to have their antidepressant discontinued and be monitored carefully for recurrence. Important factors when considering whether or not to use medications during pregnancy include severity of depressive symptoms (presence of suicidal ideations, psychosis, weight loss or malnutrition, maternal attachment), available information on the reproductive safety of the medication, prior history of depression, and response to medication treatment.

Available literature supports the safety of SSRIs and TCAs during pregnancy. The most data are available for the safety of fluoxetine during pregnancy. If choosing among the TCAs, desipramine and nortriptyline may be the agents of choice due to lower anticholinergic effects as well as decreased likelihood of worsening orthostatic hypotension. The use of TCAs offers the advantage of
easily monitored serum levels with well-studied relationships between plasma concentration and therapeutic effect. More information regarding the use of monoamine oxidase inhibitors and newer antidepressants is needed prior to recommending the use of these agents during pregnancy.

Severe depression (presence of mania, suicidality, or psychosis) during pregnancy may warrant the use of electroconvulsive therapy (ECT). ECT has been noted as a safe and effective treatment for major depression in pregnant women and is frequently considered the treatment of choice in severe depression. It should be considered that some studies have shown that women may have lower seizure thresholds during ECT than men, with men requiring higher electrical stimulus doses than women. In addition, there is also evidence that there is a potential gender difference in cognitive side effects from ECT, such as less cognitive impairment from right unilateral ECT in women compared with men.

POSTPARTUM DEPRESSION

The postpartum period appears to be a particularly vulnerable time for increased risk of the development of depressive illnesses in women. Three primary conditions have been defined in the spectrum of postpartum depressive disorder: postpartum blues, postpartum depression, and postpartum psychosis. Postpartum blues have been reported in 50%–80% of new mothers during the first 2 weeks after delivery. Symptoms of postpartum blues are time limited and include mood lability, depression, irritability, tearfulness, increased sensitivity to criticism, and alterations in sleep and appetite. Due to the time-limited nature of the symptoms of postpartum blues, management usually consists of education, support, and close monitoring. Approximately 20% of women with postpartum blues will go on to develop major depression in the first postpartum year. At the other extreme of the postpartum depressive disorder spectrum is postpartum psychosis. Postpartum psychosis is a rare condition that affects approximately 0.1% to 0.2% of new mothers. Postpartum psychosis is a severe psychiatric disorder, usually with acute onset of overt psychotic symptoms as early as the first 48 to 72 hours postpartum. Episodes of puerperal psychosis typically begin within 2 weeks of delivery and are affective in nature, usually bipolar (manic). Hospitalization and aggressive treatment may be required due to increased danger to the patients themselves or to their infants.

Postpartum depression is defined in the DSM-IV as a major depressive episode occurring within 4 weeks of delivery. The literature regarding epidemiology of postpartum depression includes a time frame ranging from 4 weeks to 6 months after delivery. This fact makes it difficult to truly establish and assess the prevalence of postpartum depression. Postpartum depression has been reported to affect between 12% and 16% of women during the 6 to 12 weeks after delivery. The risk of postpartum depression is increased to 20%–35% in women with a previous history of major depression and up to 50% in women with a previous history of postpartum depression. Other risk factors for postpartum depression include family history of depression, marital discord, stressful life events, ambivalence about pregnancy, newborn health problems, infant irritability, father’s or significant other’s emotional state, low socioeconomic state, poor social support, lack of prior experience with children, and hypothyroidism.

The etiology of postpartum depression remains a mystery. Many investigators have suggested a biologic basis for postpartum depression, but evidence to support this is insufficient. One hypothesis is that the dramatic decrease in estrogen following delivery confers additional risk of postpartum depression in vulnerable women. Changes associated with gestation and parturition involving the hypothalamic-pituitary-thyroid axis have also been postulated as contributors to postpartum depressive episodes. Rates of postpartum hypothyroidism during the first 6 months after delivery are relatively
high. Thyroiditis during the first 6 months postpartum is estimated to be as high as 9% as compared with prevalence rates of 3%–4% in the general population. Some of the mild depressive symptoms of postpartum depression have been noted to reside with normalization of thyroid function. Other potential contributing biologic factors that have been studied include gonadal hormones, prolactin, oxytocin, cortisol, and β-endorphins. No studies to date have identified any of these as specific factors in the etiology of postpartum depression.

Treatment of postpartum depression includes both nonpharmacologic therapy and pharmacologic therapy. Nonpharmacologic treatment options that are indicated as effective in postpartum depression include interpersonal psychotherapy and cognitive behavioral therapy. One study indicated that short-term cognitive behavioral therapy is as effective as fluoxetine in treatment of postpartum depression. Few studies have assessed the efficacy of antidepressant medications in the treatment of postpartum mood disorders. Fluoxetine and sertraline treatment of postpartum depression have demonstrated efficacy. There are also data to indicate that venlafaxine may also be effective in the treatment of postpartum depression. Standard antidepressant doses were effective and well tolerated with all of these agents.

Due to evidence of the contribution of direct and indirect neuromodulating effects of estrogen in affective disorders, investigators are examining the role of hormonal manipulation in the treatment of postpartum depression. To date, the use of progesterone in the treatment of puerperal mood disorders has not been shown to be effective. Some have even indicated that progesterone may exacerbate symptoms of depression in women with depressive disorders. Estrogen alone or in combination with an antidepressant should be further investigated for usefulness in the treatment of postpartum depression.

With regard to TCAs in postpartum depression, a diminished capacity to metabolize TCAs has been described during the early puerperal period. Therefore, patients should be closely monitored for adverse effects through the first 6 weeks of the postpartum period. If a woman has been treated with a TCA during her pregnancy, she should receive the same dose in the immediate postpartum period as she received prior to pregnancy.

Postpartum depression is generally treated in the same manner as major depression in women who are not pregnant. Often, physicians are more conservative with their treatment in pregnant women. A conservative approach to treatment may result in dose minimization during a time of increased dosage requirement for some antidepressants. Allowing a woman to be symptomatic during the postpartum period may lead to increased risk of relapse, recurrence, and incalculable risks to the woman and fetus.

ANTIDEPRESSANTS DURING BREAST-FEEDING

Special considerations are necessary in women who are breast-feeding. Breast-feeding is an important consideration for women during the postpartum period. Women who are breast-feeding should be counseled that all antidepressant medications are secreted in the breast milk at varying concentrations. Long-term effects of neonatal exposure to psychotropic agents are unknown. No accumulation of TCAs or sertraline in infant’s serum has been noted in studies of these drugs in breast-feeding women being treated with these agents. Collective data on serum levels suggest that infants more than 10 weeks old are at low risk for adverse effects from TCAs. There are conflicting reports of doxepin exposure, with one case report suggesting respiratory depression in an exposed infant. Fluoxetine has also had mixed reports, with case reports indicating colic, increased irritability and crying, and decreased sleep. Other reports with fluoxetine have noted no adverse effects or infant serum concentrations in infants exposed to fluoxetine through breast milk. Studies of serum levels of sertraline and paroxetine in breast-feeding mothers and their
infants indicate that these agents are secreted in breast milk, but thus far, there are no published reports indicating adverse effects in the nursing infants.\textsuperscript{41,42} Two case reports indicated that infants experienced excessive somnolence, decreased feeding, and weight loss in association with breast-feeding from a mother treated with citalopram. Some clinicians may consider the SSRIs with shorter half-lives, sertraline and paroxetine, safer in nursing mothers. Further studies are needed to investigate the use and effects of SSRIs on nursing infants.

Whether to breast-feed during antidepressant treatment is a difficult decision. Risk-benefit analysis is essential. Benefits of breast-feeding to the infant, as an ideal form of nutrition, are supported by professional organizations and available literature.\textsuperscript{25} The postpartum period is a high-risk time for the onset, relapse, or recurrence of depressive illness. Untreated depression has an adverse impact on mother-infant attachment and later infant/child development. The potential for long-term adverse effects due to chronic exposure to very low doses of antidepressants in newborns remains a primary concern. Further study of antidepressant use during the postpartum period in breast-feeding women is indicated, but can be considered if the infant is carefully monitored for adverse drug reactions such as weight loss or failure to thrive, irritability, and sedation.

\textbf{PERIMENOPAUSAL DEPRESSION AND LATE-LIFE DEPRESSION IN WOMEN}

Numerous factors such as physiological changes, menopause itself, thyroid disorders, nutritional disorders, and psychosocial issues increase the likelihood of depression in older women.\textsuperscript{27} The overall prevalence of late-life depression in the non-institutionalized elderly is 15\%, with much higher rates in some subpopulations such as Alzheimer’s disease patients (30\%–40\%).\textsuperscript{43} The longer life expectancy of women, coupled with menopause, and a greater likelihood of comorbid diseases such as dementia, diabetes, hypertension, and osteoarthritis results in depression occurring approximately twice as often in women as compared to men.\textsuperscript{44}

\textbf{Menopause}

The incidence of depression is actually thought to decrease after age 50. Depression is more likely to occur during the perimenopause period or the time between premenopause and menopause (typically between ages 45–50), because of variable estradiol levels and changes in progesterone secretion.\textsuperscript{45} Mood changes during or after menopause may be secondary to the occurrence of vasomotor and other physical symptoms rather than menopause itself. Factors that contribute to the possibility of depression during menopause include changes in family structure, financial stability, caring for aging parents, career and employment changes, children leaving and returning home, household responsibilities, and overall health. A previous history of postpartum depression, major depression, premenstrual syndrome, and prior depressive episodes are risk factors for depressive illness at menopause. Women who have surgically induced menopause also are at a particular risk for depression.\textsuperscript{46}

\textbf{Depression is more likely to occur during the perimenopause period.}
which are found deficient in depression. In women with hot flashes, depressive symptoms are 4 to 5 times more likely to be pronounced, and if there is a previous history of depression, the incidence of depression is 4 to 9 times more likely.47,48

**ENDOCRINE DISORDERS**

Depression can coexist with, or be a part of, the symptoms associated with some endocrine disorders. Subclinical hypothyroidism affects as many as 15% of elderly women. Patients with overt, mild, or subclinical hypothyroidism present more commonly with cognitive impairment and depression. It has been postulated that the common symptoms of thyroid disease, anxiety, and depression reflect central nervous system beta-adrenergic dysfunction, either as a direct result of thyroid hormone activity or as an indirect action of thyroid hormones on beta-adrenergic receptors.49

Fatigue and hypersomnia occur in both hypothyroidism and depressive disorders. Decreased appetite may also be seen in hypothyroid patients.46 Haggerty and colleagues found a greater lifetime frequency of depression in subjects with subclinical hypothyroidism (56%) than in those with normal thyroid function (20%). Those with subclinical hypothyroidism were also found to have a greater prevalence of prior depression than normal controls.49 Other endocrinological disorders associated with depression include hyperparathyroidism, hypothyroidism, pituitary disorders, acromegaly, prolactinoma, and hypopituitarism, all of which are not solely found in late-life.50

**Nutritional Disorders**

Vitamin deficiencies in older women are also associated with causing depression. Due to poor nutritional intake, deficiencies in folic acid, thiamin, riboflavin, vitamin B6, vitamin B12, vitamin C, and selenium are more likely. Alcoholism also confounds the potential for deficiencies with thiamin, folic acid, riboflavin, niacin, vitamin B6, and vitamin B12. Hypothyroid patients are more prone to deficiencies in riboflavin. Vegetarians are more likely to have deficiencies in vitamin B12 and selenium. Even the use of benzodiazepines, TCAs, and/or monoamine oxidase inhibitors can cause deficiencies in vitamins B6 and B12. Typically, depressive symptoms are present in states of deficiency, but other symptoms that occur include, but are not limited to, dementia, apathy, anxiety, irritability, confusion, and other mood-related symptoms. These deficiencies and, thus, the depressive symptoms, may be corrected with appropriate food sources and/or multivitamins.51

**Treatment Considerations in Late-Life Depression**

Treatment selection for depression in older women requires numerous physiological considerations and careful analysis of comorbid medical conditions. Women have a slower gastric emptying time, less gastric acid secretion, higher percentage of fat, decreased hepatic metabolism, and lower renal clearance compared to men. Antidepressant use in women should be selected based on its potential to cause drug interactions.27,52 The average elderly patient is taking at least 5 medications, which may include hormonal replacement therapy, treatment for osteoporosis, cardiovascular disorders, and so forth. Women who are taking hormone replacement therapy or thyroid hormones should be advised to administer the SSRIs (excluding citalopram) and nefazodone at least one hour apart from the hormones (as well as space the hormones apart from each other) to avoid delaying therapeutic effects or causing synergistic side effects. Nefazodone is a potent inhibitor of CYP4503A4, so doses of benzodiazepines, alprazolam and triazolam should be reduced by 50%–75%.53 It should also be noted that some of the metabolic products of the antidepressants are biologically active and increase the likelihood of accumulation resulting in prolonged therapeutic or side effects (i.e., fluoxetine). The older female may also be more sensitive to the effects of TCAs with a high ex-
traction ratio (i.e., desipramine, imipramine, and nortriptyline) because of decreased first-pass metabolism. The antihistamine and anticholinergic effects of the tricyclics may aggravate medical conditions like glaucoma, cardiac disorders, and seizures. Elderly women will be at a higher risk for seizures secondary to the dopaminergic effects of the tricyclics, bupropion, amoxapine, or maprotiline. The SIADH effects of the serotonin reuptake inhibitors can also increase the likelihood of seizures. Using lower doses of antidepressants may decrease the likelihood of some side effects but may also result in inadequate therapeutic response.

It is recommended to taper antidepressants to avoid withdrawal symptoms, worsening underlying depression, and rebounding of symptomatology due to abrupt discontinuation. Older women may be at a higher risk for the withdrawal effects of antidepressants because of hormonal fluctuations and deficits. Withdrawal effects are noted with the SSRIs, tricyclics, and venlafaxine.

CONCLUSION

Epidemiological studies have clearly shown a higher prevalence of major depression in women as compared to men. There is evidence that biologic and psychosocial factors play a role in differential diagnosis, assessment, and treatment of depressive disorders across a woman’s life cycle. Women may be more vulnerable to depressive symptoms during major reproductive events such as menarche, pregnancy, and menopause. There is significant evidence that serotonin is involved in disorders associated with the menstrual cycle and that serotonergic agents are effective in treating premenstrual disorders. Due to differences in pharmacokinetics, women may be more prone to adverse effects and drug toxicity as compared to men. Ongoing research will address issues regarding the role of hormones and the neuroendocrine system in depressive illnesses in women.

REFERENCES

Management of Depression in Patients with Comorbid Cardiovascular Disease

Leigh Anne Nelson and Joy R. Abu-Shanab

Evidence suggests that depression commonly occurs in patients with cardiovascular disease and is associated with a poor prognosis including increased risk of cardiac mortality. Proposed pathophysiologic mechanisms include decreased heart rate variability, altered sympathetic and parasympathetic activity, increased ventricular instability, and abnormal platelet reactivity. Other proposed mechanisms involve the interference of depression with medication adherence and cardiac risk factor reduction. Despite this evidence, depression during cardiovascular disease is commonly unrecognized and inadequately treated. Tricyclic antidepressants (TCA) are efficacious for treating depression in this population but cause serious cardiac side effects and should be avoided in patients with significant cardiovascular disease. More recent studies with bupropion and the selective serotonin reuptake inhibitors (fluoxetine, paroxetine, sertraline) indicate that they are acceptable alternatives to TCAs with regard to cardiac risk in depressed patients with heart disease, although larger studies are needed to validate their safety and efficacy in this special population. There are 3 studies currently being conducted to investigate the effect of antidepressant therapy and/or psychotherapy on cardiac morbidity and mortality in post-myocardial infarction patients with depression and/or low social support. These studies will hopefully answer the long-posed question of whether appropriate treatment of depression can improve cardiac prognosis.

KEY WORDS: depression, antidepressants, cardiovascular disease.

This article reviews the treatment trials of depression in patients with comorbid cardiovascular disease. Several epidemiological studies that have identified the significant impact that depression has on cardiovascular disease will be reviewed. The impact of depression on cardiovascular disease with regard to morbidity and mortality will be discussed. Existing pharmacoeconomic data evaluating health care costs associated with concomitant depression and heart disease will be reviewed.

A brief discussion regarding the cardiac risks associated with the tricyclic antidepressants (TCA) will be presented followed by a more in-depth review of the safety, efficacy, and drug interaction profiles of the newer antidepressants for use in depressed patients with heart disease. The design and methods of current ongoing studies directed at revealing outcomes data in regard to the use of newer antidepressants and/or psychotherapy for the treatment of depressed patients with cardiac disease and its effect on survival will be presented.

Epidemiology and Impact of Depression on Cardiovascular Disease

A study by Schleifer et al., published in the late 1980s, reported the prevalence of major de-
pression following an ischemic event to be approximately 18%. Furthermore, it was estimated that another 27% of these patients met criteria for a minor depressive episode. Approximately 44% of all of these patients continued to meet criteria for depression 3 months after the cardiac event. Other studies have reported the incidence of depression during coronary artery disease (CAD) or following an acute myocardial infarction to be between 17%–22%. The incidence of depression in the general population in any 12-month period is estimated to be 10%, which is much lower than that seen in patients with comorbid cardiovascular disease. Due to the significance of a cardiovascular event such as a myocardial infarction, depression after such an event is commonly misconceived to be normal and a situation that will disappear without intervention. Therefore, there is reluctance to diagnose patients with serious cardiovascular disease with depression and provide them with appropriate treatment. In the previously described study by Schleifer et al., only 10% of patients meeting the criteria for a major depressive episode received treatment.

Patients with cardiovascular disease may present with different depressive symptomatology as compared with a depressed patient without concurrent cardiovascular disease. One study reported that symptoms of depression in a patient with cardiovascular disease were more nonspecific in nature. Complaints of insomnia and fatigue were much more common in this population than symptoms of emotional distress such as hopelessness or suicidal ideation. This may partially explain why depression is not consistently diagnosed in this population. Although not frequently used, a cardiac depression scale has been validated for use in cardiac patients. This scale has been described as reliable, easy to administer, and more sensitive to the range of depressive symptoms commonly found in cardiovascular patients.

The relationship between depression and CAD is complex. There is evidence supporting an increased risk of death due to cardiovascular disease in patients with depression as compared with the general population. Evidence supporting this association was first reported in 1937 by Malzberg. During this time period, depression was referred to as “involutional melancholia.” Patients hospitalized in a New York psychiatric hospital from 1928 to 1931 were assessed. Death rates of patients with melancholia as compared to the general population were grouped by age in 5-year blocks. The death rates for males and females with melancholia were 6 times and 6.8 times greater, respectively, than the general population. In the population with melancholia, death rate due to cardiac disease alone was 40%, which was 8 times greater than the general population. This study is important because it was conducted prior to the availability of antidepressant drugs and therefore reflects the natural course of the disease, specifically, the effect of untreated depression on cardiovascular disease.

Even if cardiovascular risk factors are controlled for in studies, patients with depression will have a higher incidence of death due to cardiovascular disease. Anda et al. established this relationship in 1993. This cohort study included 2832 people without ischemic heart disease (IHD) and followed them for an average of 12.4 years. In this study, 11.1% were found to have depressed affect, 10.8% had moderate hopelessness, and 2.9% had severe hopelessness. In the follow-up period, 6.7% of the study population died of IHD, and an additional 9.7% were hospitalized for IHD. The adjusted relative risk for death from IHD was 1.4, 1.6, and 2.1 for depressed affect, moderate hopelessness, and severe hopelessness, respectively, when compared to patients without depression or low levels of hopelessness. The adjusted relative risk for nonfatal ischemic events was 1.6, 1.3, and 1.9 for depressed affect, moderate hopelessness, and severe hopelessness, respectively, when compared to patients without depression or low levels of hopelessness. The authors concluded that depression and hopelessness increased the risk of cardiovascular events or death from IHD independent of the...
presence of established risk factors for IHD such as family history, cholesterol levels, and smoking.

The link between depression and death from cardiovascular disease is also present in patients who have experienced a myocardial infarction and then develop depression. Mortality rates are higher for post–myocardial infarction patients who are depressed as compared with medically comparable nondepressed patients. In a landmark study by Frasure-Smith et al., 222 patients who met the criteria for a myocardial infarction from 1991 to 1992 and survived until discharge were studied. Patients underwent an interview to assess for depression between 5 and 15 days after the cardiac event. The primary objective of this study was to compare survival at 6 months between a group of post–myocardial infarction patients with depression and a nondepressed control group with similar cardiac disease. Thirty-five (16%) of the 222 patients met the Diagnostic and Statistical Manual for Mental Disorders (3rd Ed.) (DSM-III) criteria for a major depressive disorder at the time of the initial interview. At 6 months, 6 (17%) of the 35 depressed patients as compared with six (3%) of the 187 nondepressed patients had died secondary to their cardiac disease ($P = .0006$). After controlling for potential confounding factors such as ejection fraction, Killip classification, history of previous myocardial infarction, and warfarin use, the increased risk for cardiac mortality remained for patients with depression. Conclusions from this trial demonstrate that depression is clearly an independent risk factor for future cardiovascular events and death. Eighteen-month follow-up of these patients revealed nine additional deaths. Only 2 of these 9 met the DSM-III criteria for depression, but 5 of 9 had elevated Beck Depression Inventory (BDI) scores during the initial hospitalization. A diagnosis of major depressive disorder did not affect survival if patients survived more than 6 months after the initial cardiac event, but the odds ratio was 7.8 for those who died of cardiac disease more than 6 months after the initial cardiac event and had a BDI score of 10. This study did not answer the question of whether treatment of depression can decrease or negate this association.

Depression during the post–myocardial infarction period has a significant negative impact on functional status and the ability to adhere to cardiac rehabilitation plans. The presence of depressive symptoms following an ischemic event has been correlated with a decreased effect on the maintenance of healthy behavior changes during and after the rehabilitation period (smoking cessation/exercise class/lifestyle changes). Studies have found that depressed patients were 40% less likely to stop smoking, more likely to quit exercise programs, and experienced greater stress and social difficulties after a myocardial infarction. In a study by Steffens et al., 335 hospitalized patients with CAD were interviewed with regard to functional capacity. This process included evaluation of the patient’s ability to perform activities of daily living (basic self-maintenance tasks) as well as instrumental activities of daily living (such as preparing meals, doing yard work, managing finances, etc.). The presence of depression in patients with CAD was associated with significant deficits in the ability to complete activities of daily living and instrumental activities of daily living resulting in increased functional impairment as compared with a nondepressed control group. Although one cannot assign a direct causal relationship from this trial alone, this degree of functional impairment should be of great concern to all health care providers.

**PROPOSED MECHANISMS FOR INCREASED MORTALITY IN DEPRESSED PATIENTS WITH CARDIOVASCULAR DISEASE**

There are several proposed physiologic mechanisms linking depression to an increased risk of CAD. They include reduced heart rate variability, alteration in the ratio of sympathetic to parasympathetic tone, increased ventricular instability, as well as an elevation in
platelet reactivity. Heart rate variability (HRV) is the variation between R to R intervals in sinus rhythm and reflects the balance between the sympathetic and the parasympathetic systems. In healthy hearts, a high degree of variation is seen; however, in patients with CAD, the variation decreases, and this has been correlated with an increased risk of sudden death after an acute myocardial infarction in several studies.16–21 HRV can be used along with other factors such as decreased left ventricular function, advanced age, or presence of an arrhythmia after an acute myocardial infarction to predict risk of death.

It is also proposed that changes in the balance of sympathetic to parasympathetic tone toward a sympathetic predominance may cause depressed patients with cardiac disease to be more susceptible to sudden cardiac death due to a lowered threshold for ventricular arrhythmias.22 Although studies have reported mixed results, some have shown that patients with depression have increased levels of circulating norepinephrine (NE), which again puts them at increased risk for ventricular arrhythmias.23–25 It is proposed that the effects of increased sympathetic tone lead to changes within the heart and blood vessels as well as to changes to the platelets.

Abnormal platelet activity, including increased platelet reactivity, in patients with depression is also reported to be a potential contributing factor to the increased risk for ischemic events.26 It has been shown that platelet factor 4 (PF4) and β-thromboglobulin (β-TG) levels are increased in patients with depression and ischemic heart disease when compared to patients with either condition alone.27 These factors are released into the bloodstream when platelets are activated to recruit other platelets and promote platelet aggregation with subsequent thrombus formation. This phenomenon would help to explain why depressed patients with ischemic heart disease experience more events than nondepressed controls. Only 1 study to date has evaluated the effect of antidepressant treatment on platelet activity.28 Depressed patients with ischemic heart disease were randomly assigned to receive either nortriptyline or paroxetine. Platelet activity as measured by levels of PF4 and β-TG was assessed at baseline and after treatment. The paroxetine group showed a marked reduction in the concentration of both PF4 and β-TG, whereas this effect on platelet activity was not seen in the nortriptyline-treated group. The results of this study suggest that a differential response on platelet activity exists with antidepressants with differing mechanisms of action, which may correlate to a change in outcome for the patients. Research evaluating platelet function during depression thus far suggests that there is an increase in platelet reactivity regardless of cardiovascular history, and this heightened activity may correlate with an increased likelihood of thrombus formation, especially in those patients with concurrent cardiovascular disease.

**Depression has been related to poor adherence to therapy recommendations after an acute myocardial infarction.**

As previously discussed, depression has been related to poor adherence to therapy recommendations after an acute myocardial infarction.12,13 It is thought that this may contribute to the increased risk of nonfatal and fatal ischemic events in this population. A study published by Carney et al. found that depressed patients’ adherence rate to prophylactic aspirin therapy was only 45% as compared with an adherence rate of 69% for nondepressed patients (P < .02).29 Zeigelstein et al. conducted a study to determine if depression was associated with a reduction in adherence to therapy intended to reduce cardiovascular risk.30 They recruited a total of 204 patients admitted to the hospital with an acute myocardial infarction. The patients were assessed using the BDI. Thirty-five (17.2%) of the 204 patients enrolled in the study were found to have BDI scores ≥ 10, re-
flecting at least mild depression. Major depression or dysthymia was diagnosed in 31 (15.2%) of the 204 patients using the DSM-III-R. The authors found that patients with either a BDI score ≥10, major depression, or dysthymia were significantly less likely to report adherence with low-fat diet, regular exercise, stress reduction, and regular social interaction for support than did their nondepressed counterparts. The depressed patients also reported being less likely to adhere to medication regimens as prescribed. Of the 18 patients known to have died by 4 months, 7 (38.9%) had a BDI score of ≥10 during hospitalization (P < .04 when compared to other groups). This finding did not reach statistical significance for patients with major depression and/or dysthymia due to patients lost to follow-up and a relatively small sample size. These factors may explain in part why depression is linked with a worse long-term prognosis after an acute myocardial infarction.

FINANCIAL IMPACT OF DEPRESSION WITH CARDIOVASCULAR DISEASE

Research to date has indicated that there is an increase in cardiovascular events in patients with depression. It is also of interest whether this population consumes more health care dollars than nondepressed counterparts. Two studies to date have evaluated the financial impact of depression on cardiovascular disease.31,32 The most recent study, published last year, was conducted by Frasure-Smith and colleagues and evaluated the effect of post–myocardial infarction depression on health care costs using the Quebec Medicare database.32 Data from patients used in previous studies were analyzed. A total of 848 patients who survived 1 year after a myocardial infarction and had completed the BDI during the initial cardiac hospitalization were included. During the initial hospitalization, 30.7% of patients had a BDI score ≥ 10, which reflects at least mild to moderate symptoms of depression. Costs associated with the index admission and those occurring during the first year after discharge were compared between the depressed group and a nondepressed group. Health care costs associated with the initial admission were 11% higher in the depressed group as compared with the nondepressed group. This primarily reflected a longer length of stay on the inpatient unit for the depressed patients. Health care costs for the year following a myocardial infarction, excluding the index admission, were 41% higher in the depressed group as compared with the nondepressed group (P = .004). This increase in health care dollars spent did not reflect a change in the need for cardiac procedures but rather an increase in emergency room visits and visits to physicians. These increased office visits constituted on average 2 extra office visits per year and interestingly were not accounted for by use of psychiatric services. This study suggests that in addition to the decrease in survival for patients with depression after an acute myocardial infarction that there is also an increase in health care expenditures for the index cardiac admission and during the first year after the event.

TREATMENT OF DEPRESSION IN PATIENTS WITH CARDIOVASCULAR DISEASE

Antidepressant Treatment Trials

Although evidence supporting an association between depression and poor prognosis in cardiovascular disease continues to accumulate, data supporting a relationship between the treatment of depression and improved survival are sparse. Only 1 study to date has addressed this issue.33 Avery and Winokur conducted a case-control study involving 519 depressed patients who were hospitalized between 1959 and 1969.33 Patients were followed for a 3-year period. The study found mortality secondary to nonsuicidal deaths, specifically myocardial infarction, occurred significantly more often in the group receiving inadequate treatment (antidepressant or electroconvulsive therapy) for their depression than in the group receiving ad-
equate treatment. It is possible the group that received inadequate treatment for their depression also received inadequate treatment for their other disease states, so concluding with certainty that treatment of depression decreased nonsuicidal mortality is not possible. Regardless, there is evidence that antidepressant therapy is effective for depressed patients with cardiovascular disease. Therefore, depressed patients with heart disease should receive adequate treatment to relieve suffering and improve their quality of life.

There is a paucity of data examining the pharmacological treatment of depression in patients with comorbid cardiovascular disease. The most studied class of antidepressants with regard to cardiovascular effects is the TCAs. Initial studies focused solely on safety issues surrounding TCA use in patients with heart disease. This concern stemmed from evidence that deaths secondary to TCA overdoses were a direct result of cardiac complications, such as conduction blocks or arrhythmias. Subsequent studies addressed both efficacy and safety issues regarding the use of TCAs in patients with various cardiovascular diseases. These studies supported the efficacy of TCAs for the treatment of depression in this special population and also better defined the cardiovascular risks associated with their use. The following cardiovascular side effects were associated with TCA use in these studies: elevated heart rate, orthostatic hypotension, atrioventricular node and intraventricular conduction delay, bundle branch block, complete heart block, and ventricular tachyarrhythmia. Most of these studies were conducted prior to the availability of newer antidepressants such as the selective serotonin reuptake inhibitors (SSRI), which have relatively benign cardiovascular side effect profiles in healthy adults. Therefore, the benefit of treating depression in a patient with comorbid heart disease with a TCA outweighed the risk of cardiovascular side effects or the risks associated with untreated depression, most importantly suicide. This belief held true until the early 1990s, when the results of the Cardiac Arrhythmia Suppression Trial II (CAST II) were made known. The CASTs were designed to determine whether the common practice of suppressing ventricular premature depolarizations with antiarrhythmic agents following a myocardial infarction decreased cardiovascular mortality. The first CAST trial was prematurely discontinued after 2 years due to increased cardiovascular mortality associated with type 1C antiarrhythmic drugs, encainide and flecainide, as compared with placebo. TCAs possess type 1A antiarrhythmic activity similar to the antiarrhythmic agent moricizine or quinidine. Prior to CAST II, it was thought that the use of TCAs in patients with significant heart disease might have provided some cardiovascular protection based on its antiarrhythmic activity in addition to its antidepressant properties. Moricizine was included as a study drug in the original CAST and was the focus of CAST II. CAST II was designed to further evaluate the role of type 1A antiarrhythmic agents, specifically moricizine, in post–myocardial infarction patients with premature ventricular contractions. Again, this study was stopped prematurely due to increased cardiovascular mortality in the moricizine-treated group as compared with the placebo group (2.5% vs. 0.5%; \( P = .001 \)). Based on the results of a meta-analysis, quinidine has also been shown to increase cardiovascular mortality in similar patient populations. Therefore, this adverse effect on cardiovascular mortality was extrapolated to include all drugs that possessed class 1A antiarrhythmic activity including the TCAs. Based on these findings, the risks of using TCAs in patients with significant cardiovascular disease now appeared to outweigh the benefit, and there was increased interest in finding
acceptable alternatives to manage depression in this population.

Bupropion was the first alternative to TCAs to be studied in depressed patients with comorbid cardiovascular disease. Several studies confirmed the cardiac safety of bupropion in depressed patients without significant comorbid illnesses. Only 2 studies have examined the safety of bupropion in depressed patients with comorbid cardiovascular disease. The first study was a double-blind, crossover study evaluating the safety of bupropion as compared with imipramine in 10 depressed patients with congestive heart failure. The average bupropion dose was 445 ± 16 mg/day. Neither drug adversely affected any indices of left ventricular function including ejection fraction. Severe orthostatic hypotension occurred in 50% of the participants treated with imipramine resulting in drug discontinuation. As expected, based on its lack of affinity for the α-1 receptor, bupropion was not associated with orthostatic hypotension. Bupropion increased supine systolic blood pressure by an average of 4 mmHg, but this was not considered a clinically significant finding. The study concluded that bupropion was a safe alternative to imipramine in depressed patients with comorbid congestive heart failure. An obvious limitation of this study is the small sample size, which would limit extrapolation of these results to the general population of patients with congestive heart failure.

The second study, conducted by the same authors, was a prospective, open-label trial assessing the safety of bupropion in 36 depressed patients with various cardiovascular disease states (congestive heart failure, conduction disturbances, arrhythmias). Cardiac assessments occurred at baseline and following 3 weeks of bupropion treatment and included the following parameters: radionuclide angiography to assess left ventricular ejection fraction, standard 12-lead ECG to measure PR and QRS intervals, and 24-hour ambulatory ECG to assess ventricular arrhythmias, mean 24-hour pulse rate, and higher degree AV block in patients with bundle branch block. In addition, supine and standing blood pressures were measured 3 times daily. The average bupropion dose was 442 mg ± 47 mg/day. The study found no statistically or clinically significant changes in pulse rate, left ventricular function, or cardiac conduction. Bupropion significantly increased supine systolic and diastolic blood pressures. The average increase in systolic blood pressure was 5 mmHg (P < .01), and the average increase in diastolic blood pressure was 3 mmHg (P < .005). The authors reported that this increase was not considered clinically significant, but 2 of the 36 patients enrolled in this study dropped due to significant worsening of systolic hypertension. A cause-and-effect relationship was suspected as the hypertension resolved in both patients and returned to baseline levels after discontinuation of bupropion. In addition, bupropion was associated with statistically significant orthostatic hypotension. Again, the authors state that this finding was not clinically significant, but 1 patient developed symptomatic orthostatic hypotension resulting in a fall and was dropped from the study. Orthostatic hypotension resolved in this patient after the bupropion was stopped for only one day. The authors concluded that this study preliminary evidence supporting the use of bupropion as an alternative to TCAs in the treatment of depressed patients with comorbid cardiac disease. They also supported the need for further studies evaluating the use of bupropion in this population that were of longer duration and involved more participants in order to confirm their findings. These types of studies have never been conducted.

Three of the 5 SSRIs available in the United States (fluoxetine, paroxetine, and sertraline) have been evaluated for the treatment of depression in patients with comorbid heart disease. Fluoxetine was evaluated in a prospective, open-label study involving 27 depressed patients with the following comorbid cardiac disease states: impaired left ventricular function, ventricular arrhythmias, and/or conduction disease. Fluoxetine’s effect on cardiovascular function was compared with the cardiovascular effects previously identified.
with nortriptyline, a representative TCA. Participants received fluoxetine up to 60 mg/day for a 7-week period. The cardiac assessments used in this study were similar to those used in the bupropion study previously described and included the following: radionuclide angiography to assess left ventricular ejection fraction, standard 12-lead ECG and 24-hour ambulatory ECG to assess heart rate and rhythm and conduction disturbances, and supine and standing blood pressure. These parameters were assessed at baseline and at the end of weeks 2 and 7. At the end of week 2, fluoxetine was found to decrease heart rate by 6% (P = .0002), whereas nortriptyline increased heart rate by 9% (P = .04). This specific adverse effect is important based on the increased cardiac workload placed on the heart as heart rate increases and may be related to a poorer prognosis. Although fluoxetine increased supine systolic blood pressure by 2% (P = .02), this increase was not clinically significant. No other effect on blood pressure was seen with fluoxetine. Furthermore, fluoxetine did not induce orthostatic hypotension, prolong the QRS or QTc intervals, or cause conduction disturbances of any kind. In patients with a baseline ejection fraction of ≤ 50%, fluoxetine increased the ejection fraction by 7% (P = .05). The clinical significance of this finding is unknown. There was a substantial drop-out rate for both groups. Eight (30%) of the 27 patients in the fluoxetine group did not complete the study with only 1 of these dropouts due to a cardiovascular adverse event. This event did not resolve with discontinuation of fluoxetine. Cardiac adverse event rate for the nortriptyline group was 20% with 12 of the 15 dropouts experiencing a cardiac event. These included orthostatic hypotension, worsening arrhythmias, acute myocardial infarction, conduction disturbances (including AV blockade), worsening congestive heart failure, and intolerable anticholinergic side effects including tachycardia. There were 2 deaths in the nortriptyline treatment group and none in the fluoxetine group. The authors concluded that fluoxetine had a favorable cardiac side effect profile in depressed patients with heart disease and was not associated with adverse cardiac events as seen with the TCAs in this population. The authors accurately identify the short duration of the study and the small sample size as limitations. In addition, the heterogeneous composition of cardiac disease states included in this small sample size makes it difficult to extrapolate the results to any one specific cardiovascular disease.

Based on the safety data presented in this study, it would appear that fluoxetine would be a preferred antidepressant to a TCA in this patient population. This is misleading because there were no efficacy data presented in this paper, although it was collected and published 4 years prior to this publication. The intent-to-treat response rate for fluoxetine was 23%. The response rate for patients with melancholic depression was only 10% in the fluoxetine group. This is compared to an intent-to-treat response rate of 67% for nortriptyline-treated patients and an 83% response rate for nortriptyline-treated patients with melancholic depression. This study concluded that fluoxetine was significantly less effective than nortriptyline for the treatment of depression of the melancholic subtype and comorbid cardiovascular disease. Although fluoxetine possesses a favorable cardiac profile, it may not be the most appropriate antidepressant choice for a patient with comorbid heart disease and severe melancholia.

Roose and colleagues published the first prospective, multicenter, randomized, double-blind study comparing the efficacy and safety of paroxetine versus nortriptyline in the treatment of depression in patients with comorbid ischemic heart disease. To be included in this study, patients met the DSM-IV criteria for a major depressive episode, unipolar subtype, and had score of ≥16 on the 17-item Hamilton Rating Scale for Depression (HRSD). In addition, patients met the following criteria for IHD: history of myocardial infarction, coronary artery bypass graft surgery, or coronary angioplasty or had a positive stress test or angiographic evidence of a 75% or greater luminal narrowing of a major coronary artery.
or one of its branches. Patients were excluded from the study for the following reasons: myocardial infarction within the past 3 months, baseline QTc interval > 460 msec, unstable or crescendo angina, and current use of warfarin or a drug with class 1 antiarrhythmic activity. The following baseline cardiac assessments were conducted: 24-hour continuous ECG, standard 12-lead ECG, radionuclide angiography, and supine and standing blood pressures. These parameters were assessed at baseline and at the end of weeks 2 and 6. Clinically stable patients entered a 2-week placebo period. At the end of the placebo period, 81 patients still meeting the inclusion criteria were randomized to 1 of the 2 treatment groups using permuted blocks of 10. Paroxetine was titrated up to a maximum of 40 mg/day, while nortriptyline was titrated to achieve a therapeutic blood level of 50–150 ng/ml. Treatment response was defined as ≥ 50% reduction in HRSD score and a final HRSD score of ≤ 8. An intent-to-treat analysis found a 61% (25/41) response rate in the paroxetine group as compared with a 55% (22/40) response rate in the nortriptyline group. No statistical analysis was presented for these data. At the end of week 2, paroxetine increased heart rate by 4 bpm (P < .03), but this effect was not present at the end of week 6. At the end of week 6, paroxetine increased supine systolic blood pressure by 4 mmHg (P < .03), but this was not considered to be clinically significant. No other cardiac parameters were affected by paroxetine. Although nortriptyline did not adversely affect cardiac conduction in this study, it did induce a significant increase in 24-hour heart rate by 11% (P < .001) and increased supine and standing pulse rates by 12% (P < .001) at the end of week 6. This effect on heart and pulse rates was a sustained effect as it was also present at the end of week 2. The dropout rate due to side effects was significantly higher in the nortriptyline group as compared with the paroxetine group (P < .03). Only 1 patient in the paroxetine group was suspected of experiencing an adverse cardiac event resulting in study discontinuation as compared with 7 patients in the nortriptyline group. The authors concluded that both drugs were effective for treating depression in patients with IHD, but paroxetine was associated with a lower rate of serious adverse cardiac events as compared with nortriptyline. The authors appropriately identified the small sample size and relatively stable IHD, as limitations in the study. These results would be difficult to extrapolate to patients with more severe IHD, such as that seen in the immediate post–myocardial infarction period.

It is established that there is a positive correlation between increased heart rate in patients with IHD and mortality; that is patients with increased heart rates have increased mortality. Based on this knowledge and recognition that antidepressant therapy would be expected to extend well beyond 6-weeks’ duration, studies evaluating the long-term effects of antidepressant use in patients with IHD are needed.

The Sertraline Antidepressant Heart Attack Trial trial was a prospective, open-label, multicenter, pilot study to assess the efficacy and safety of sertraline use in depressed patients after an acute myocardial infarction. SSRIs have been associated with bleeding most likely due to their effect on platelet function as reported in the literature by several case reports and a small pilot study. The potential of bleeding as a complication of SSRI treatment raises concerns for patients recovering from infarction. This study was designed to specifically assess the effect of sertraline on cardiovascular and hemostatic function, risk of adverse events, and mood in 26 depressed patients recovering from a myocardial infarction. Patients meeting the DSM-IV criteria for a major depressive episode within 5 to 30 days after experiencing a myocardial infarction. Patients meeting the DSM-IV criteria for a major depressive episode within 5 to 30 days after experiencing a myocardial infarction were included in the study. Patients were excluded for the following reasons: pending heart transplantation, pacemaker-defibrillator placement, or coronary artery bypass grafting; left ventricular ejection fraction < 35%; current treatment with antidepressants or lithium; history of nonresponse to sertraline; or substance abuse or dependence within 6 months of the myocar-
dial infarction. The following safety parameters were used in this study: radionuclide ventriculography for left ventricular ejection fraction, 24-hour ambulatory ECG and standard 12-lead ECG, supine and standing blood pressure, prothrombin time reported as the International Normalized Ratio, partial thromboplastin time, and bleeding time. The HRSD, BDI, and the Clinical Global Improvement Scale (CGI) were used to assess efficacy. Following a 1-week single-blind placebo run-in period, patients received sertraline up to 200 mg/day. The mean time from the occurrence of the myocardial infarction to initiation of sertraline was 30 ± 12 days. Nineteen (73.1%) of the 26 patients completed the entire 16 weeks of the study. Only 3 patients discontinued treatment due to adverse events. Adverse events of concern included abnormal bruising, angina, and myocardial infarction. There were no deaths in the study, and the myocardial infarction was not attributed to sertraline by the authors. The mean sertraline dose was 79.8 ± 38.7 mg/day with only 2 patients receiving doses >100 mg/day. There were no significant changes in heart rate or supine and standing blood pressure at the end of 16 weeks as compared to baseline. Sertraline did not induce orthostatic hypotension or significant changes in left ventricular ejection fraction or cause conduction disturbances of any kind. Coagulation measures were not significantly altered by sertraline. Although not significant, bleeding time increased in 12 patients and decreased in 2 patients. Treatment response was defined as ≥50% decrease in HRSD score. Based on this threshold, 74% of patients at the end of week 16 were defined as treatment responders. HRSD scores decreased from a mean baseline score of 19 ± 6.2 to 9.8 ± 8.6 (P < .001). The BDI and CGI also reflected significant improvement in depression as compared with baseline (P < .001). The study concluded that sertraline was associated with clinical improvement in depression and was well tolerated with a low risk for adverse cardiac events. Although this study had many limitations, it served its purpose to provide preliminary data to support a larger, randomized, placebo-controlled study to further evaluate the role of sertraline for treatment of depression after an acute myocardial infarction. This study, the Sertraline Anti-depressant Heart Attack Recovery Trial (SADHART), is currently underway. The study is sponsored by the company that manufactures and markets sertraline. It is a multicenter, prospective, randomized, parallel-group, double-blind, placebo-controlled study of 26 weeks’ duration. It is anticipated that this study will enroll a total of 600 depressed patients who are acutely recovering from a myocardial infarction and provide recommendations regarding the treatment of depression in this medically unstable population including cardiac survival as an outcome.

Currently, there are no studies evaluating the efficacy and safety of the newer antidepressants such as venlafaxine, nefazodone, mirtazapine, and citalopram specifically in patients with comorbid cardiac disease. Venlafaxine has been associated with an increase in diastolic blood pressure. Although venlafaxine has never been studied in depressed patients with comorbid cardiac disease states, its safety has been assessed in older patients with significant medical comorbidities such as head injury, hypertension, stroke, or IHD. In this study, venlafaxine was not associated with any significant sustained changes in blood pressure when given at doses of 50–250 mg/day. Changes in diastolic blood pressure were no more likely to occur in older patients with comorbid illnesses as compared with younger patients. The study concluded that venlafaxine was a safe and effective antidepressant in both young and older patients with medical comorbidities. Venlafaxine’s effect on blood pressure is reported to be dose related. The doses evaluated in this study would be considered low to moderate as the maximum recommended dose is 375 mg/day. Results of this study could not be extrapolated for patients receiving venlafaxine at doses >250 mg/day. Regardless of these results, all patients receiving venlafaxine should have their blood pressure
monitored periodically. This is especially true for patients with comorbid cardiovascular disease states where the induction or worsening of hypertension could significantly affect morbidity and mortality.

In addition to the SADHART, 2 additional studies regarding the management of depression in cardiac patients are currently underway.\textsuperscript{61,62} The Myocardial Infarction and Depression-Intervention Trial is a multicenter, prospective, randomized study being conducted in the Netherlands.\textsuperscript{61} The purpose of this trial, similar to the SADHART, is to investigate the effect of antidepressant treatment for post-myocardial infarction depression on cardiac prognosis. The study received funding from the Netherlands Heart Foundation and 2 pharmaceutical companies. It is estimated that approximately 2200 patients experiencing a myocardial infarction between September 1999 and March 2002 will be enrolled in this trial and screened for depressive symptoms at 0, 3, 6, 9, and 12 months post–myocardial infarction. Those patients diagnosed with depression will be randomized to the intervention group or the “care as usual” group. Patients in the intervention group will receive either placebo or mirtazapine. Citalopram will be used as a second-line agent for the intervention group in an open-label fashion. Cardiac prognosis will be assessed for both groups by comparing the incidence of new cardiac events, including hospital admissions of a cardiac nature and cardiac death. Again similar to the SADHART, the goal of this study would be to provide evidence supporting the treatment of depression and a favorable cardiac prognosis and provide recommendations regarding antidepressant use in this special population.

The National Heart, Lung, and Blood Institute sponsored the second study, the Enhancing Recovery in Coronary Heart Disease Patients.\textsuperscript{62} The purpose of this multicenter, randomized trial was to investigate the effect of psychosocial interventions for depression and/or low social support or isolation on the risk of reinfarction and cardiac survival in post–myocardial infarction patients. Patients with depression and/or minimal social support were randomized to either a group receiving psychosocial interventions, including individual cognitive behavioral therapy and group therapy, or a group receiving usual care. Patients with severe depression in the intervention group were allowed to receive antidepressant therapy with sertraline. Approximately 3000 patients were enrolled in this study between October 1996 and October 1999. Strengths of this study design included the following: (1) average follow-up duration was 3 years, (2) inclusion of a high-risk population with depression and/or minimal social support, and (3) inclusion of a large enrollment of females and minorities in the study. Results of this study are yet to be published.

**Drug Interactions**

Although the newer antidepressants previously reviewed in this article have a low cardiac risk profile, they are associated with drug interactions of concern for patients taking cardiovascular medications. It is likely that patients with cardiovascular disease will be taking multiple chronic medications for their disease management including antihypertensives, antiarrhythmics, anticoagulants, antihyperlipidemics, and other miscellaneous drugs such as digoxin, which increases their risk of drug interactions. The SSRIs are potential inhibitors of the cytochrome P450 (CYP) enzyme system, which is responsible for the metabolism of the majority of medications on the market.\textsuperscript{63} Fluoxetine and/or its active metabolite, nor-fluoxetine, are inhibitors of the following CYP enzymes: CYP2D6, CYP3A4, CYP2C9, and CYP2C19.\textsuperscript{63} Paroxetine inhibits only CYP2D6.\textsuperscript{63} Sertraline is a weak inhibitor of CYP2D6 and CYP2C19.\textsuperscript{63} Bupropion and venlafaxine have minimal impact on the CYP system.\textsuperscript{63} A list of cardiovascular medications reported to be metabolized by different CYP enzymes can be found in Table 1.\textsuperscript{63–65} The coadministration of an enzyme inhibitor with a specific substrate could result in an exaggerated pharmacological response and increased
side effects or toxicity. This is especially true for drugs that are primarily metabolized by 1 specific pathway. For example, many of the calcium channel blockers (CCBs) are primarily metabolized by CYP3A4. If an inhibitor of CYP3A4, such as fluoxetine, was added to the drug regimen of a patient stabilized on a CCB, the patient would be at risk for hypotension and associated symptoms. Although these newer antidepressants have a low cardiac risk associated with their use, a patient’s cardiovascular disease may be worsened as a result of a drug interaction. Therefore, it is important to be knowledgeable of these drug interactions and experienced in their management.

CONCLUSION

Depression has been shown to adversely affect morbidity and mortality in patients with cardiovascular disease. Although there is an abundance of evidence to support this link, it continues to be underrecognized and inadequately treated. Although effective, TCAs have a serious cardiovascular side effect profile and are not recommended for use in patients with significant cardiovascular disease. Studies have shown that the SSRIs have an acceptable safety profile for use in this population, but data regarding efficacy are limited. Based on current data, the SSRIs should be considered first-line therapy for all patients including those with cardiovascular disease. Bupropion and venlafaxine would be appropriate second-line therapy for those patients who fail initial treatment with an SSRI. Regardless of these recommendations, it is important to tailor drug selection to the patient including previous positive antidepressant response or family history of treatment response. Future studies with the newer antidepressants in patients with cardiovascular disease should provide more evidence to support safety and justify a relationship between treatment of depression and reduction of mortality.

REFERENCES


36. Raskind M, Veith R, Barnes R, et al. Cardiovascular and antidepressant effects of imipramine in the treat-
Depression among Patients with HIV/AIDS: A Treatment Dilemma

Gerald P. Overman and Stacey L. Anderson

Increased longevity of HIV-infected individuals due to expanding pharmacological research allows a longer period of time for mood disorders to come to medical attention. A longer period of time exists in which the treatment of depression can make a difference in the quality of life, function, and course of HIV infection. Many HIV-related symptoms and concurrent treatment regimens can complicate the choices made regarding mood disorder treatments. Certain HIV/AIDS patients are at greater risk for developing depression, such as those with substance abuse/dependence. Differentiation between the clinical presentation of depression in the general population versus the HIV/AIDS population is important. Although differentiating between symptoms of depression, somatic complaints, and cognitive deficits may be difficult, specific symptoms in HIV-infected individuals prevail. Substantial evidence suggests that antidepressant therapy and psychotherapy are effective in most HIV-positive patients with major depression. One of the greatest difficulties in drug selection for the HIV-infected population is the avoidance of clinically significant drug-drug interactions between antidepressants and antiretrovirals. Evaluating the tolerability of antidepressant medications is also an important factor of effective treatment. This article attempts to clarify all the aforementioned issues pertaining to treatment choices in HIV-infected individuals suffering from depression.

KEY WORDS: HIV, depression, substance abuse, antidepressant.

INTRODUCTION

The prevalence of psychiatric manifestations among patients with HIV/AIDS creates profound diagnostic and treatment dilemmas. Shock, denial, guilt, anger, and anxiety accompany the discovery of seroconversion. Many patients adjust overtly to this crisis within several weeks or months. Others, however, develop a myriad of other important clinical, social, legal, and ethical problems, including depression and substance use disorders.2,3

Although the recent advent of pharmacological breakthroughs has led to a better quality of life for HIV/AIDS patients who have access to them, there remains a plethora of lifestyle and socioeconomic changes of major consequence. This increased longevity allows a longer period of time for psychiatric symptoms to come to medical attention, especially prior to AIDS, and provides a longer period of time in which the treatment of depression can make a difference in the quality of life, function, and course of HIV infection. Untreated depression in HIV infected individuals can compromise adherence to medication regimens, leading to the progression of HIV illness. Depression has been associated with decreased immune function, and some evidence suggests that it may also be associated with increased mortality in HIV-infected individuals.4
DIAGNOSTIC ISSUES

Of particular importance is the influence of a diagnosis of HIV/AIDS on mood, specifically the development of depression. The Diagnostic and Statistical Manual of Mental Disorders, (4th ed.) (DSM-IV),5 offers specific criteria for several mood disorders that may develop after the diagnosis of HIV/AIDS. Mood disorder due to a general medical condition is a prominent and persistent disturbance in mood that is judged to be due to the direct physiological effects of a general medical condition. Though the clinical presentation may resemble that of a major depressive episode, the full diagnostic criteria must not be met. Two specific subtypes related to depressed mood exist within DSM-IV criteria. They include (1) with depressive features and (2) with major depressive-like episode. These refer to patients whose predominant mood is depressed but the full criteria is not met, and those who meet full criteria except for the exclusion of a general medical condition or substance-induced cause of symptoms. The reader is referred to the full criteria for major depressive episode presented earlier in this issue of the journal. Adjustment disorder is applied when symptoms occur within 3 months of the onset of an identifiable stressor, which resolves within 6 months of the termination of that stressor (or its consequence). Regardless if the comorbid diagnosis of major depressive disorder, depression due to a general medical condition, or adjustment disorder is made among patients with HIV/AIDS, the need for treatment with antidepressant therapy should be considered.

Cognitive impairment is one of the more common and feared complications of HIV infection.6 Although it has been noted in all stages of HIV infection, cognitive impairment usually appears during the later stages of the disease. The most common initial symptoms are decreased attention, decreased concentration, and difficulty in shifting cognitive tasks. Associated behavioral changes include increased irritability, apathy, and decreased desire for social contact. Concomitant neurological impairment, including gait abnormalities and lack of coordination of the upper extremities, may also exist. The common terms are HIV-associated cognitive impairment and the more severe HIV dementia. It is extremely important to evaluate patients for symptoms of cognitive decline when assessing for the presence of a depressive disorder. The differential diagnosis of cognitive impairment is listed in Table 1.

PREVALENCE

Conflicting data exist regarding the prevalence of major depressive disorder in the HIV/AIDS population. Several limitations of these epidemiological studies include varying definitions and assessment techniques, diverse clinical samples, differences in risk factors, differences in stages of infection of the participants, and differences in study design. Eight different studies have reported a prevalence of depression in HIV/AIDS patients from 22%–45% compared to prevalence between 5% and 15% in the general population.7–12 Thus, despite the limitations of these studies, the prevalence of depression appears to be greater in persons infected with HIV versus the general population.

Table 1. Differential Diagnosis of Cognitive Impairment6

<table>
<thead>
<tr>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early to midstage HIV disease</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Alcohol and substance abuse</td>
</tr>
<tr>
<td>Medication-induced cognitive impairments</td>
</tr>
<tr>
<td>Metabolic encephalopathies</td>
</tr>
<tr>
<td>HIV-related cognitive impairment</td>
</tr>
<tr>
<td>Advanced HIV disease (CD4+ &lt; 100 mm³)</td>
</tr>
<tr>
<td>Opportunistic infection of CNS</td>
</tr>
<tr>
<td>Neurosyphilis</td>
</tr>
<tr>
<td>CNS lymphoma</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Metabolic encephalopathies</td>
</tr>
<tr>
<td>Medication-induced cognitive impairments</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>HIV dementia</td>
</tr>
</tbody>
</table>

Abbreviations: CNS—central nervous system.
DISEASE PROGRESSION

Depression may alter HIV disease progression by impairing immune function or influencing patient behavior. Findings have been inconsistent in studies assessing the influence of depression on immune function. However, several studies have found associations between stress, depression, and alterations in immune response. For example, stress and depression can cause reductions in the number of natural killer cells and CD8+ T cells with CD4+ T helper cells being less affected.13,14 Published studies on the relationship between depression and HIV/AIDS mortality remain inconclusive, reporting inconsistent results.15–17 Firm conclusions about the validity of these trial results cannot be made without considerably more large-scale cohort studies. Depression may also affect the progression of HIV illness indirectly by altering patient adherence to medication regimens. Contributors to poor adherence as a consequence of depression include feelings of self-neglect, apathy, and forgetfulness.18 Poor adherence to HIV medication regimens can result in suboptimal response and disease progression. Depression may be a modifiable risk factor for poor adherence and should be actively targeted for treatment to limit disease progression.

Stress and depression may have a negative impact on the progression of HIV disease, however, there is inconclusive evidence suggesting that HIV disease negatively affects the progression of depression. Clinical studies suggest that depression rates do not increase as HIV disease progresses, however, a limitation of these studies is that most study participants were either asymptomatic or only mildly symptomatic throughout the period of observation.7,19 No relationship has been found between measurements of depression, psychiatric distress, or psychosocial stresses and immune status or HIV illness stage. Also, a relationship between depression and HIV RNA viral load could not be found. Therefore, one can conclude that cumulative evidence from several clinical trials does not support an increased rate of depression with advanced HIV disease.

RISK FACTORS

Several risk factors have been identified for the development of depression in HIV/AIDS patients.20,21 These risk factors include having a history of depression, being a homosexual man, being a woman, being an intravenous drug user, and having multiple HIV medications. HIV-positive individuals who have had depression in the past are especially susceptible to recurrences. Data suggest that rates of depression are equal between HIV-positive and noninfected homosexual men. Thus, homosexuality may be a predisposing factor independent of HIV serostatus. Contributing factors to depression in HIV-positive homosexual men include social stigmatization, loss of friends to HIV disease, and isolation from social support. Higher rates of depression occur in women, independent of HIV serostatus. It is unknown whether HIV-positive women have higher rates than noninfected women. No study has been conducted investigating the mood effects of HIV medication. It may be difficult to distinguish between the psychological impact of the initiation of antiretroviral therapy and the actual chemical effects of the medication; therefore, case reports may represent idiosyncratic rather than common mood effects. Table 2 lists medications that may contribute to depressive symptoms.22

SYMPTOMATOLOGY

It is important to differentiate between the clinical presentation of depression in the general population and the clinical presentation in the HIV/AIDS population. Despite the similarity in depressive symptoms between HIV-infected and noninfected patients, depression is more often underdiagnosed in the former group. Depression may be underdiagnosed in HIV-positive individuals because some symptoms, such as fatigue, decreased appetite, and decreased libido can be attributed to HIV disease itself.23 Several somatic symptoms of HIV disease overlap with symptoms of depression.
Table 2. Selected P450 Drug Interactions with HIV/AIDS Therapy and Antidepressants\(^{43,46-47}\)

<table>
<thead>
<tr>
<th>Isoenzyme</th>
<th>Substrate</th>
<th>Inducer</th>
<th>Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2B6</td>
<td>bupropion</td>
<td>rifampin</td>
<td>delavirdine efavirenz isoniazid ritonavir fluconazole ketoconazole sulfamethoxazole</td>
</tr>
<tr>
<td>CYP2C9/10</td>
<td></td>
<td>ritonavir</td>
<td>fluvoxamine fluoxetine sertraline</td>
</tr>
<tr>
<td>CYP2C9/10</td>
<td>rifampin</td>
<td>fluoxetine fluvoxamine sertraline</td>
<td></td>
</tr>
<tr>
<td>CYP2C19</td>
<td>imipramine clomipramine citalopram (metabolite)</td>
<td>nelfinavir</td>
<td>ampronavir delavirdine efavirenz ketoconazole ritonavir</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>imipramine clomipramine citalopram (metabolite)</td>
<td>nelfinavir</td>
<td>ampronavir delavirdine efavirenz ketoconazole ritonavir</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>citalopram (metabolite) paroxetine sertraline venlafaxine nefazodone trazodone clomipramine desipramine imipramine nortriptyline doxepinmaprotiline</td>
<td>codeine hydrocodone meperidine morphine methadone oxycodone tramadol dextromethorphan amphetamines heroin</td>
<td>efavirenz propoxyphene ritonavir</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>amitriptyline clomipramine imipramine desipramine nortriptyline trimipramine citalopram mirtazapine nefazodone sertraline</td>
<td>clarithromycin erythromycin cocaine fentanyl methadone THC acetyaminophen corticosteroids delavirdine dapsone efavirenz estrogen indinavir nevirapine ritonavir rifabutin rifampin hypericum</td>
<td>fluvoxamine fluoxetine sertraline paroxetine fluconazole ketoconazole itraconazole metronidazole azithromycin clarithromycin erythromycin ampronavir indinavir nelfinavir saquinavir efavirenz delavirdine grapefruit juice</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>amitriptyline clomipramine desipramine imipramine</td>
<td>caffeine</td>
<td>ritonavir smoking fluvoxamine fluoxetine paroxetine sertraline</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>amitriptyline clomipramine desipramine imipramine</td>
<td>caffeine</td>
<td>ritonavir smoking fluvoxamine fluoxetine paroxetine sertraline</td>
</tr>
</tbody>
</table>

\[^{43,46-47}\] Reference(s)
such as low energy, fatigue, poor sleep, and decreased appetite.\textsuperscript{24–26} Somatic symptoms can make the diagnosis of depression difficult, therefore, it is important to investigate whether other cognitive and emotional symptoms of depression are present. Depression and cognitive deficits, or dementia, can occur simultaneously in HIV-positive patients.\textsuperscript{26,27} Impairments in psychomotor functioning and memory are more common in dementia than depression, while depression is more associated with impairments of attention and concentration. Mood and cognition can also be negatively affected by opportunistic infections, such as cryptococcal meningitis and toxoplastic encephalitis. Other symptoms, such as agitation, depressed mood, and insomnia can be linked to medications commonly used by these patients. Neuropsychiatric assessment tools can be extremely helpful in this situation.

Although differentiating between the symptoms of depression, somatic complaints, and cognitive deficits is important, there is a prevalence of specific symptoms in HIV disease.\textsuperscript{26,27} In general, signs and symptoms of depression in HIV-infected individuals are similar to noninfected persons. However, there may be a difference in the prevalence of certain symptoms. HIV-infected patients complain of sleep and appetite disturbances more frequently than noninfected patients. Decreased energy and libido are more frequent among noninfected individuals. In the early stages of HIV illness, physical symptoms such as low energy, fatigue, poor sleep, and poor appetite rarely coexist with depression. During the early, asymptomatic stage of HIV infection, cognitive changes should be attributed to depression, whereas in advanced HIV infection or AIDS, a dual assessment of depression and cognitive dysfunction should be attempted. Several experts advise focusing on affective or cognitive symptoms that reflect mood state alone for a more reliable diagnosis.\textsuperscript{27} These symptoms include sadness, lethargy, anhedonia, irritability, guilt, and suicidal ideation.

**TREATMENT**

\textit{Pharmacological}

There is substantial evidence suggesting that antidepressant therapy is effective in most HIV-positive patients with major depression. Adherence to antiretroviral medication regimens is paramount for the effective treatment of HIV disease. Due to the potential cross-tolerance and the inflated number of pills HIV-positive patients take per day, evaluating the tolerability of antidepressant medications may be the most important factor of effective treatment. Guidelines on the course and duration of treatment of depression in the general population can be applied to the HIV-infected population. A difficult choice lies in antidepressant drug selection. Several studies have been conducted using tricyclic and nontricyclic antidepressant agents in HIV-infected persons with major depression. Alternative agents such as psychostimulants and androgens have also been studied.

Five studies were conducted using tricyclic antidepressants (TCAs) for the treatment of depression in HIV-infected individuals.\textsuperscript{28–32} Response rates were similar to those studies in noninfected individuals who were medically healthy taking similar doses. Patients responded equally well regardless of their stage of HIV infection. No studies showed an alteration in CD4+ T cell counts for imipramine or desipramine. CD4 count declines were typical over time for reported disease progression rates. Despite efficacy, anticholinergic adverse effects such as constipation, dry mouth, dizziness, and hypotension may limit TCA use in this population. These anticholinergic effects were responsible for nearly 50% of antidepressant discontinuations. The second most common reason for drug discontinuation was in-
increased pill burden. The incidence of confusion and memory impairment with TCAs may also limit use in patients with HIV-associated cognitive impairment or dementia. Other disadvantages of TCAs include potential need for serum drug level monitoring, overdose toxicity, and gradual dosage adjustment upon initiation. The anticholinergic and antihistaminic adverse effects of TCAs may provide an advantage in special populations of HIV-infected individuals, such as those persons experiencing chronic diarrhea, insomnia, weight loss, and/or neuropathic pain.

Serotonin selective reuptake inhibitors (SSRIs) and other non-TCAs have also been studied. Seven studies of fluoxetine found response rates anywhere from 64%–100%.33–39 Other non-TCAs studied include sertraline, paroxetine, nefazodone, and fluvoxamine.29,39–43 Like TCAs, response rates are similar to those seen in the general population. SSRIs do not appear to negatively affect CD4 counts and are equally efficacious at all stages of HIV infection. SSRIs are generally better tolerated than TCAs with the most frequent side effects of nausea, diarrhea, upset stomach, headache, dry mouth, and nervousness. Sexual dysfunction was not a major reason for discontinuation in the HIV-positive population. Fluvoxamine was associated with the greatest number of severe adverse effects. Nine of 16 patients taking fluvoxamine in one clinical trial discontinued therapy due to adverse events, however, a large initial dose of 100 mg every evening may have contributed to this high discontinuation rate. Published trials using venlafaxine and bupropion in HIV-positive patients are lacking, but these agents may be considered for use. Mirtazapine may also be considered for use in the HIV population. Its primary adverse effects are sedation and increased appetite, which may be beneficial in some HIV-positive individuals. Mirtazapine causes minimal nausea, insomnia, and sexual dysfunction and lacks potential for clinically significant drug-drug interactions through the CYP450 system.

Psychotherapy has also been proven effective in clinical trials for the treatment of depression in HIV-infected persons.44 It has been shown that psychoeducation about depression may increase adherence to medication regimens in this population. Interpersonal therapy is effective for individual psychotherapy, and all group psychotherapy modalities appear to be equally effective. Modalities that reduce stress are useful in reducing depressive symptoms as well.

Drug Selection

One of the greatest difficulties in drug selection for the HIV-infected population is the avoidance of clinically significant drug-drug interactions between the antidepressants and the antiretrovirals. Despite a great potential for drug interactions between these agents, few
clinical studies have documented these interactions in humans. Many of the antiretrovirals affect concentrations of antidepressants, which may compromise their efficacy. All 4 protease inhibitors and the non-nucleoside reverse transcriptase inhibitor delavirdine inhibit CYP3A4 to various degrees. Therefore, antidepressants with primary routes of metabolism that involve CYP3A4, such as nefazodone, are likely to be affected. Ritonavir is the most potent inhibitor of CYP3A4. Systemic concentrations of TCAs may increase 1.5- to 3-fold with concomitant ritonavir administration. Therefore, these patients should be monitored for worsening of TCA adverse effects as well as signs of toxicity. Other antidepressants with serum concentrations that should be expected to rise 1.5- to 3-fold with concomitant ritonavir include venlafaxine, trazodone, paroxetine, and possibly fluvoxamine. Bupropion is contraindicated for concomitant use with ritonavir due to a potential increase in seizure activity through a CYP3A4 interaction. However, recent data suggest bupropion is mainly metabolized through CYP2B6. Clinical data on this interaction is lacking. Nefazodone and ritonavir taken concomitantly resulted in marked confusion, dizziness, intense anxiety, headache, disorientation, derealization, and agitation in one patient during clinical trials. Therefore, nefazodone is probably a poor choice for patients receiving ritonavir unless lower dosages (50–100 mg/day) are used. Ritonavir, although a potent inhibitor, may also induce CYP3A4, making drug interactions unpredictable. In addition, ritonavir is also an inducer of CYP1A2 and an inhibitor of CYP2D6. Nevirapine is an inducer of CYP3A4 as well, which may compromise the efficacy of anti-depressants metabolized by this isoenzyme. Efavirenz may inhibit or induce CYP3A4.

Antidepressants may affect concentration of HIV medications as well. For example, fluvoxamine and nefazodone, both potent inhibitors of CYP3A4, may increase protease inhibitors or non-nucleoside reverse transcriptase inhibitor serum concentrations, such as nelfinavir. Alternative therapies for the treatment of depression, such as St. John’s wort, can cause clinically significant drug-drug interactions with the antiretroviral agents. St. John’s wort (hypericum) is an inducer of CYP3A4, thereby potentially decreasing serum concentrations of protease inhibitors and non-nucleoside reverse transcriptase inhibitors, reducing antiretroviral efficacy. This interaction has yet to be tested in clinical investigations. Many other medications that HIV-positive patients take for prophylaxis and treatment of opportunistic infections are metabolized by the CYP450 system as well. Table 2 lists clinically significant CYP450 drug-drug interactions between antidepressant and antiretroviral agents.

Antidepressants may affect concentration of HIV medications as well.

SUBSTANCE USE DISORDERS AMONG DEPRESSED HIV/AIDS PATIENTS

Intravenous drug use is the largest area of interest within the substance-abusing AIDS population because of the obvious relationship to the transmission of HIV. Recreational use of nonparenterally used substances is also of great importance with respect to their behavioral effects on transmission (i.e., high-risk sexual behaviors). More important to this discussion is the detrimental effect of substance use disorders (SUDs) on the treatment of comorbid depression among HIV/AIDS patients. Terminology in the field of addiction is a very complex and confusing issue. For this discussion, SUD will refer to substance abuse, substance dependence, addiction, as well as alcoholism. HIV-positive patients with a current SUD report more depression, more distress, and a diminished quality of life than HIV-positive patients without a current SUD. Similarly, patients with depression report higher rates of SUDs than nondepressed individuals. These higher rates underscore the importance of diag-
nostic and treatment intervention among HIV/AIDS patients with the comorbidities of depression and SUD. The remainder of this section will discuss important clinical issues related to the dual diagnosis of depression and SUD.

Prevalence rates of dual diagnosis are difficult to determine and are dependent on the population studied. Overall prevalence rates for SUD among private and public psychiatric populations is approximately 50%, with specific prevalence rates among depressive disorders of 30%. However, when evaluating psychiatric disorders among SUD populations, prevalence rates are considerably lower. The prevalence rate of depressive disorders among SUDs is 5%. See Table 3 for a list of prevalence rates for the major psychiatric disease states and SUDs. One explanation for this discrepancy is that the exclusionary criteria, such as effects of recent substance use and induced disorders (intoxication and withdrawal) for depressive disorders are applied more stringently in addiction populations and settings. Another explanation is the presence of similar symptomatology. Psychiatric symptoms from SUD occur more commonly than independent coexisting psychiatric disorders in patients with SUD. An example is the presence of depressive symptoms during a “cocaine crash” or withdrawal from cocaine. During the early stages of cocaine withdrawal, many symptoms mimic the symptoms of major depressive disorder. However, after approximately 30 days postwithdrawal, the prevalence of symptoms consistent with a diagnosis of major depressive disorder are as prevalent as those found in the general population.

The important dilemmas facing the clinician treating patients with dual diagnosis are numerous, the least of which are the determination of the most appropriate, individualized treatments and the lack of cohesion between addiction and psychiatric models of care. The Institutes of Health defines the scope of the problem, posing the question: “which kinds of individuals, with what kinds of alcohol/drug problems are likely to respond to what kinds of treatments by achieving which kinds of goals when delivered by which kinds of practitioners?” Patients with dual diagnosis complicated with HIV/AIDS add to these complex treatment questions. Although clinicians generally agree that all patients with SUD require significant support, the kind of treatment that is effective remains undefined. Project MATCH, a large, well-defined treatment-assessment program in the United States, examined the effectiveness of matching 3 important psychosocial interventions to individual patient types. The types of therapy included 12-step facilitation, cognitive-behavioral and motivational enhancement therapy. The ability to match patients to specific psychotherapies to enhance treatment outcomes was not achieved, but all 3 strategies were found to be efficacious.

Three treatment models exist among the dually diagnosed: the serial treatment model, the parallel model, and the integrated model. The serial treatment model is the most commonly used. In the serial treatment model, addiction treatment generally follows psychiatric stabili-

<table>
<thead>
<tr>
<th>Diagnosis: Comorbidity</th>
<th>Prevalence Rate: Psychiatric Setting*</th>
<th>Prevalence Rate: Addiction Setting**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive disorders</td>
<td>30</td>
<td>5.0</td>
</tr>
<tr>
<td>Bipolar disorders</td>
<td>50</td>
<td>0.8</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>50</td>
<td>1.1</td>
</tr>
<tr>
<td>Antisocial personality disorders</td>
<td>80</td>
<td>2.0</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>30</td>
<td>3.0</td>
</tr>
<tr>
<td>Phobic disorders</td>
<td>25</td>
<td>6.0</td>
</tr>
</tbody>
</table>

*Percentage of patients diagnosed with comorbid addictive disorder.
**Percentage of patients diagnosed with comorbid psychiatric disorder.
zation. Limitations of this model include a physical separation between staff and milieu and a lack of referrals to addiction treatment after psychiatric stabilization. With the parallel model, treatment of both disorders occurs simultaneously. There remains a physical separation of staff and milieu. Treatment with the parallel model works well with the full cooperation of all staff involved. Potentially, the most effective model of treatment of the dually diagnosed individual is the integrated model. A core treatment team provides treatment for both the SUD and psychiatric disorder, staff are trained in both areas, and denial in both areas is not only lessened but is also better confronted.

SUDs can further complicate the treatment of depression.

and treated. Major limitations of the integrated model are undertreatment of addictive disorders and overdiagnosis of psychiatric disorders. The integrated approach has great potential utility among patients with HIV/AIDS as an additional confounding issue. Regardless of the treatment model exercised, diligence and concern are required to appropriately treat this difficult patient population. Future important research includes matching patients not only to psychotherapeutic strategies with various treatment models but also to pharmacological therapies as well.51

CONCLUSION

The prevalence of depression appears to be greater in persons with HIV infection versus the general population. Untreated depression in HIV-infected individuals can compromise adherence to medication regimens, leading to progression of HIV illness. With the importance of adherence to antiretroviral medication regimens, evaluating the tolerability of antidepressant medications may be the most important factor of effective treatment. SSRIs and newer agents may be more tolerable, however, an evaluation of these antidepressants for potential drug interactions should be conducted to avoid potential adverse events in the HIV-positive population. SUDs can further complicate the treatment of depression among the HIV/AIDS population. Ideal management includes recognition and treatment of both as primary disorders with an ideal setting uses an integrated, dual-focused treatment program. There is a burgeoning of information regarding the pharmacological treatment of SUDs, depression, and HIV/AIDS. An appropriate treatment regimen will take into account individual patient and disease state characteristics, as well as potential medication adverse events and drug interactions.

REFERENCES


Considerations for the Use of Alternative Therapies in the Treatment of Depression

Angela M. Emanuel, Thea R. Moore, and Patty Ghazvini

Approximately 65%–75% of patients with major depression will respond to drug therapy. However, conventional antidepressants may be costly and have side effects and drug interactions that may inconvenience the patient, limit the use of the particular drug, or require the discontinuation of a particular therapy. In this past decade, there has been a renewed interest in alternative medicines, especially for depression, that are available without a prescription. The ability of patients to self-medicate depression presents a risk of inappropriate treatment, thereby increasing the morbidity and mortality rates associated with this sometimes fatal disease. In addition, herbal products are not regulated by the government, leading to problems with batch-to-batch consistency and adulteration, even for products that have evidence of efficacy in depression. The potential for herbal-pharmaceutical grade drug interactions increases the need for input and follow-up from health care practitioners. There is limited quality evidence describing the efficacy and optimal dosing for these products. Clinicians must acknowledge that patients are using herbal products and educate on their use to avoid negative outcomes in patients with depressive disorders.

KEY WORDS: alternative therapies, depression, herbals, St. John’s wort, Sam-E, mood.

INTRODUCTION

Approximately 19 million people will experience a depressive episode in any given year, but only a third of these patients actually seek medical treatment. It is estimated that by the year 2020, major depression will be the second most important cause of disability worldwide. Eisenberg and associates found that between 1990 and 1997, nearly 41% of adults who had severe depression and anxiety used alternative therapies within 12 months of their diagnosis. There are several hypotheses that explain the lure of using alternative approaches instead of Food and Drug Administration (FDA)—approved or conventional antidepressants. Cultural traditions, lack of governmental regulation, accessibility, adverse effects of pharmaceutical-grade products, drug interactions, and stigma associated with certain mental disorders all contribute to patients seeking alternative treatment. More than $4–$6 billion are spent on these therapies annually. Pharmacists should be an integral part of the educational process for patients and practitioners because of the potential of drug-herbal interactions, disease exacerbations, and adverse reactions that could result from use of these products. This article will discuss and examine the benefits and risks associated with the use of herbal medicinals for treating depression.
Herbal Therapies as Primary Treatment for Depression

St. John’s Wort
(Hypericum perforatum)

_H. perforatum_ is the most popular herbal product used to treat mild to moderate depression. _H. perforatum_ is the dried herb of the flowering top of a member of the St. John’s wort family, native to Europe and naturalized in Asia, Africa, North America, South America, and Australia. It was so named because the blooms are at their brightest golden-yellow color coincidentally with the feast day of John the Baptist on June 24.

Ancient Greeks used _H. perforatum_ as a diuretic, wound-healing herb and for treatment of menstrual disorders. Today, _H. perforatum_ is used orally for the treatment of mild to moderate depression. Externally, the oil is used for the treatment of wounds, abrasions, and first-degree burns.5–8

There are various proposed mechanisms of action for _H. perforatum_, although the precise mechanism is unclear. Hypericum extracts contain more than 10 constituents that could provide its antidepressant effects including napthodianthrones (i.e., hypericin and hyperforin), flavanoids (i.e., quercetin), xanthones, and bioflavanoids. Hypericin and pseudohypericin have demonstrated considerable antiretroviral activity in both in vitro and in vivo testing, which are believed to help inhibit viral infections, especially retroviruses such as HIV and herpes. Hyperforin is a potent inhibitor of serotonin, dopamine, noradrenalin, and gamma aminobutyric acid. It is not clear whether hyperforin inhibits the reuptake and synthesis or affects neurotransmitter receptors otherwise. The flavonoids and xanthone components may be responsible for monoamine oxidase inhibition.6–12

_H. perforatum_ is available in a variety of dosage forms including capsules, tablets, teas, and extracts; however, the extract is most commonly employed for treating depression.5 The extract LI 160 has been associated with clinical efficacy for depression.8 A hypericin content of 0.3% is the standard for pharmaceutical quality of the _H. perforatum_ extract. This standardization may not offer any guarantee of pharmacologic benefit, as hypericin may not be the primary active constituent, and the active components of hypericum teas cannot be standardized. Most studies disregard the activity of hyperforin and adhyperforin. The fruits of the plants are not typically harvested in the extract form, and they are unstable when exposed to heat and light. Most of hyperforin and adhyperforin are found predominantly in the reproductive parts of the plant (2% in the flowers, 4.5% in the unripe fruits, and 4.4% in ripened fruits).6–10

Adverse effects of _H. perforatum_ are mild compared to conventional antidepressants. In an open-label study of 3250 patients, the most common side effects noted over a 4-week period were gastric-related symptoms, allergic reactions, and fatigue. Photosensitivity reactions were first observed in cattle grazing in Europe but have been noted in fair-skinned individuals and patients receiving injectable forms of _H. perforatum_. Other adverse effects associated with hypericum include dry mouth, dizziness, constipation, confusion, drowsiness, lethargy, peripheral neuropathy, and restlessness.6,7 Despite its proposed monoamine oxidase and serotonin-reuptake inhibiting action, there have been no reports of hypertensive crisis, cardiotoxicity, or sexual dysfunction.

The dose of _H. perforatum_ most commonly used is 300 mg two to three times a day, taken with water at mealtime. Studies suggest that adults with mild to moderate depression will benefit from 0.9–2.7 mg of hypericin/day. Higher doses of up to 1800 mg/day have been studied in individuals with severe depression.
No studies have been done on children to date. In 1984, the German Commission E monographs cited hypericum as an experimental monoamine oxidase inhibitor in daily doses of 2–4 grams/day or 0.2–1.0 mg/day of total hypericin. Despite these citations, clinicians should remember that these monographs were translated from dated German medical practices that may not be applicable to current medical practices. Despite a number of studies, pharmacokinetic data are limited. The t1/2 of hypericin and pseudohypericin is around 24 hours, which implies that the extract may be administered once daily. Antidepressant effects are not reported to occur until after 2 to 4 weeks of continuous treatment.10

H. perforatum has been compared to placebo, maprotiline, imipramine, amitriptyline, desipramine, and bromazepam in clinical studies. More than 3000 patients have been evaluated for clinical efficacy of the extract and injectable formulations. A meta-analysis of randomized clinical trials suggests that H. perforatum extracts were superior to placebo and similarly effective as standard antidepressants. Unfortunately, none of the studies were longer than 12 weeks.21,22 Larger studies comparing the extract to more contemporary antidepressants and doses are needed.

There have been no human studies evaluating the teratogenic effects of hypericum. Anecdotal reports in humans suggest that hypericum may be safe during pregnancy. Animal studies suggest that prenatal exposure causes no long-term deficits in growth, physical maturation, or future reproduction compared to placebo. It is noted that hypericin and pseudohypericin cross the placenta, so it is not recommended for women using hypericum to breast-feed.13

Drug interactions are of concern when patients take H. perforatum. Reports have been documented that suggest that H. perforatum is a potent inducer of the cytochrome P4503A metabolic pathway and may increase metabolic activity 2-fold, resulting in decreased plasma concentrations of other medications when taken concomitantly.14–17 Yue and associates reported on 8 females who were taking either cyclosporine, theophylline, ethinylestradiol/desogestrel, or warfarin. Three of the patients had decreased serum concentrations of cyclosporin. One patient had a lowered concentration of theophylline. Three of the females taking ethinylestradiol/desogestrel experienced breakthrough bleeding. The last patient had a lowered serum concentration of warfarin. Interestingly, there have been at least 7 reports of reduced anticoagulant effects when H. perforatum is coadministered with hypericum since 1999, so it is recommended to monitor bleeding time and INR when using the two together. At least 8 cases of intermenstrual bleeding or change in menstruation were reported in women ages 23 to 32. All of the women were taking oral contraceptives with hypericum.6,18 Other important interactions include reduced concentrations of digoxin, some of the steroidal hormones, and HIV-1 protease inhibitors.17–20

Additive toxicity with other antidepressants may occur resulting in serotonin syndrome–like reactions. There have been reports that this syndrome is characterized by mental status changes, tremor, gastrointestinal upset, headache, myalgia, and restlessness. The syndrome has also occurred when H. perforatum was taken with selective serotonin reuptake inhibitor antidepressants or nefazodone.6,14 Because of these risks, clinicians should consider a 5 to 7 day wash-out period when switching between conventional antidepressants. In moderate to severely depressed patients, a gradual cross-titration is recommended.

Although studies imply that H. perforatum is efficacious compared to tricyclic antidepressants, more research is needed comparing it to other antidepressants, and further evaluation of its exact mechanism of action is needed to min-
imize adverse effects like serotonin syndrome. Its side effect and drug interaction profile also should be considered in patients taking other medications.

Sam-E (S-adenosylmethionine)

S-adenosylmethionine has been marketed as a promising alternative to St. John’s wort. It is known in European countries as ademetione and is used for the treatment of depression, arthritis, cholestasis, fibromyalgia, and migraine headaches. S-adenosylmethionine, unlike H. perforatum, is naturally produced by the body and is involved in a number of biochemical pathways. It was first discovered in the 1950s, but due to its lack of chemical stability, it was not studied in clinical trials until 20 years later in the injectable form of the stable salt. In 1999, General Nutrition Companies, Inc. and Pharmavite Corporation marketed mass production of an enteric-coated oral formulation as a nutritional supplement.15,23,24

S-adenosylmethionine is found in every cell in the body, particularly in the brain and liver, and is essential to numerous metabolic processes in the body. The synthesis of S-adenosylmethionine is directly linked to folate and vitamin B metabolism. Deficiencies in these vitamins are associated with reduced concentrations of S-adenosylmethionine in central nervous system (CNS) and neuropsychiatric disorders.24

Animal studies suggest that the antidepressant effects of S-adenosylmethionine may be due to an increase of the turnover of catecholamines (norepinephrine, serotonin, and dopamine) and weak effects on monoamine oxidase. Intravenous administration resulted in suppressed orthostatic rise in pulse rate and decreased plasma norepinephrine. Levels of 5-hydroxyindoleacetic acid were elevated in the cerebrospinal fluid of depressed patients who received injections of S-adenosylmethionine, suggesting activation of the central serotonergic system. It appears to inconsistently inhibit monoamine oxidase type B in the brain but increases monoamine oxidase activity in the heart and brain tissue. All of these effects could theoretically improve the mood.15,23

There have been studies comparing the injectable form of S-adenosylmethionine to other antidepressants and using it as augmentation. Intramuscular and intravenous administration of S-adenosylmethionine proved to be more significantly effective than placebo; however, the enteric-coated oral formulation is the only form available in the United States. A metaanalysis of 6 placebo-controlled clinical trials in a total of 200 patients and 7 trials, concluded in 3 weeks or less, showed that S-adenosylmethionine was at least as effective as imipramine, desipramine, amitriptyline, or clomipramine and more effective than placebo. Although the studies were placebo controlled, the short duration and lack of appropriate psychometric testing make the results unreliable.15,23,24

The usual dose of S-adenosylmethionine recommended for depression is 200–800 mg twice daily. Most of the published studies used doses of 1600 mg/day. The bioavailability of S-adenosylmethionine is low, implying that the oral administration results in a significant first-pass effect. S-adenosylmethionine is metabolized by the liver but does not bind to plasma proteins. No drug interactions have been reported as of yet between S-adenosylmethionine and other drugs. After intravenous doses of 50 mg/kg in humans, the half-life is approximately 80 minutes, with urinary metabolites being noted after 48 hours and fecal tracings noted after 72 hours.23

There are less adverse effects and drug interactions with use of S-adenosylmethionine compared to H. perforatum. The most common adverse effects include gastrointestinal discomfort such as flatulence, nausea, vomiting, diarrhea, anxiety, and headache. A switch to hypomania was reported in a few patients by Carney and associates.23

S-adenosylmethionine may have a role in treating depression, but more studies are needed comparing it to conventional therapies.
outside of the tricyclic antidepressants as well as comparing it to *H. perforatum* and other herbals.

**DHEA (Dehydroepiandosterone)**

DHEA is an endogenous hormone secreted by the adrenal cortex and is a precursor to androgenic steroids. It is synthesized de novo by the CNS, and concentrations are found higher in the brain compared to other organs. It is commonly known as the “fountain of youth,” and is used as a natural aphrodisiac. Although DHEA is considered a banned substance, athletes use DHEA for its anabolic effects. The over-the-counter sale of DHEA was banned by the FDA in 1984 due to concern over hepatotoxicity. The Dietary Safety Health and Education Act of 1994 allowed DHEA to be marketed as a nutritional supplement, although its true nutritional value is doubtful.

DHEA is promoted for possible antidepressant effects because of its excitatory activity on gamma aminobutyric acid (GABA) and NMDA. Bloch and colleagues found that DHEA may have antidepressant effects in patients with midlife-onset dysthymia and major depression. There have been at least 2 case reports linking DHEA to manic episodes in patients with no previous psychiatric history. Wolkowitz and associates showed >50% decrease in Hamilton Depression Rating Scale scores in 5 of 11 patients with major depression compared to 11 patients given placebo. Since more rigorous studies are needed to establish doses, clinical efficacy data, and information regarding drug interactions and side effects of DHEA, it is not recommended to use this product as first line for the treatment of depression.

**HERBALS AS ADJUNCTIVE THERAPIES**

Other herbal therapies are commonly used as adjunctive treatments in depression because depression often involves sleep disturbances and anxiety. It is common practice for patients to combine herbal remedies such as kava kava and valerian root with each other, with *H. perforatum*, or with prescription antidepressant agents, increasing the risks of drug interactions. The bulk of evidence in the literature exists for valerian and kava, primarily for use as sedatives and/or anxiolytics.

**Valerian**

The plant name for valerian is *Valeriana officinalis*. Valerian has been also referred to as garden heliotrope, all heal, amantilla, and set wall. Valerian is commonly indicated for insomnia and anxiety and possibly as an anticonvulsant. Active ingredients are thought to include volatile oil (sesquiterpines), iridoids (valepotriates), and alkaloids.

The mechanism of action of valerian is proposed to be inhibition of the breakdown of GABA. Valerian may also have an affinity for the serotonin 2a (5HT2a) receptor. Valerian may affect calcium entry or binding in muscle tissue. Of the valepotriates, valtrate and isovaltrate have antidepressant properties, and the didrovaltrate has a tranquilizing effect similar to that of the benzodiazepines.

Precautions for the use of valerian are similar to those with benzodiazepines, barbiturates, and other CNS depressants. The significance of interaction between alcohol and valerian is still under evaluation; therefore, caution is advised with the combination of valerian and alcohol. Valerian has also been shown to prolong thiopental- and pentobarbital-induced sleep. Patients should also be cautioned when driving or operating machinery. Valerian should be avoided during pregnancy and lactation.

Adverse effects associated with the use of valerian include headaches, hangover effects,
excitability, insomnia, uneasiness, and cardiac disturbances. Ataxia, decreased sensibility, hypothermia, hallucinations, and muscle relaxation have also been noted with valerian therapy but are not common. The recommended dosage is typically 2–3 g of the dried herb or extract 1 to 3 times per day and at bedtime. Valerian is also used as a tea with 2–3 g per cup, 1 to 3 times daily. Recommended dosage of the tincture is 0.5–1 teaspoons (1–3 mL) 1 to 3 times per day.

Valerian should not be considered for use in patients receiving CNS-depressing medications. There are limited studies evaluating its efficacy in depressed patients. Further study is needed to determine the exact role of valerian adjunctively with other herbals in the treatment of depression.

**Kava Kava**

Kava kava, or simply kava, is derived from the root of the pepper plant, *Piper methysticum*, which is found in the South Pacific islands and Australia. Kava is also known as ava, intoxicating pepper, and ava pepper. Kava is commonly prepared as a ceremonial beverage, which acts as a CNS depressant that causes a tranquil state of intoxication. Kava is primarily indicated as an anxiolytic and sedative.

Kava is also said to promote sociability in a similar manner as alcohol. Kava has also been reported to have anticonvulsant and muscle relaxant properties, but these are not as well supported in the scientific literature. The primary active ingredients in kava are thought to be kavalactones (α-pyrones). The mechanism of action for kava is proposed to be binding at GABA and benzodiazepine receptor sites. Kava was reported to produce changes in the electroencephalogram similar to those produced by diazepam.

Adverse effects associated with chronic, high-dose use of kava include scaling of the skin on the extremities, eye disturbances, muscle weakness, and vitamin B deficiency. Kava use has also resulted in hepatotoxicity, macrocytosis of the red blood cells, neurologic effects, anorexia, and pulmonary hypertension. Extrapyramidal symptoms and exacerbation of Parkinson’s disease have been reported with the use of doses of 100–450 mg/day. Clinical trials with kava have used doses of standardized preparations (WS 1490) that typically contain 100–200 mg of kavalactones, given daily in divided doses or as a single dose at bedtime. The recommended adult daily dose is 60–120 mg kava pyrones.

Potential drug interactions with kava include synergistic sedative activities with alcohol and prescription sedative/hypnotics. Kava may be detrimental to cognitive function. There is one case report of a drug interaction between alprazolam and kava. A 54-year-old man was hospitalized in a lethargic and disoriented state. The patient’s medications included alprazolam, cimetidine, and terazosin. An interaction between kava and alprazolam was thought to be the most likely explanation of the patient’s condition. Kava is contraindicated in pregnancy and lactation. The use of kava kava is not recommended in patients taking concomitant benzodiazepines, and further study is needed to establish its exact role in treating depression.

**Passionflower**

Passionflower is made from the plant *Passiflora incarnata* and is also called apricot vine, grenadille, maypop, passiflora, and passion vine. Passionflower is noted to possess sedative, hypnotic, antispasmodic, and analgesic properties. The proposed mechanism of action of passionflower is monoamine oxidase inhibition, leading to central stimulant activity.
This action is commonly attributed to the active constituent of harman alkaloid. The sedative effects of the maltol and ethylmaltol constituents are thought to mask the stimulant actions of the alkaloids.\textsuperscript{5,29}

Adverse effects associated with passionflower use include hypersensitivity vasculitis and altered consciousness.\textsuperscript{4,5,29} Due to sedative effects, the usual precautions regarding operation of machinery and driving of motor vehicles should be observed. Use during pregnancy and lactation is not recommended.

Passionflower is typically given 3 times daily in doses of 0.25–1 g of dried herb, 0.5–1 mL of liquid extract (1:1 in 25\% alcohol), or 0.5–2 mL of tincture (1:8, 45\% alcohol).\textsuperscript{5,29}

It is not known if passionflower will interact with tyramine-containing foods and other medications that conserve catecholamines, so caution should be exercised in the use of passionflower for depression.

**Skullcap**

Plants of the species *Scutellaria lateriflora*, commonly referred to as skullcap, helmet flower, hoodwort, quaker bonnet, and scutellaria, are often used in Chinese medicine. Skullcap is indicated for use as a sedative and anticonvulsant. The mechanism of action and active constituents of skullcap remain unclear.

Adverse effects associated with skullcap include giddiness, stupor, confusion, and seizures. Hepatotoxic effects have also been reported, but these may have been attributable to ingredients of the preparation in the particular case.\textsuperscript{4,5} Skullcap use is not recommended during pregnancy and lactation due to its hepatotoxic effects and limited information about pharmacological activity (lack of clinical trials in humans).\textsuperscript{5}

Skullcap is taken 3 times daily in doses of 1–2 g of dried herb, 2–4 mL of liquid extract, and 1–2 mL of the tincture.\textsuperscript{5}

There are no studies proving the clinical efficacy of adjunctive use of skullcap for insomnia associated with depression.

**Hops**

Although hops (*Humulus lupulus*) is commonly known for its use by the brewing industry to produce beer, the female flowers of the plant have a long history of medicinal use as a mild sedative. The sedating effects of hops are thought to be due to volatile oil constituents. Active ingredients increase when the herb is stored for 1 to 2 years. Adverse effects associated with hops include respiratory allergy, contact dermatitis, and disruption of the menstrual cycle. The sedative action of hops may potentiate the effects of other sedative therapies or alcohol. It has been stated that hops should not be given to those suffering from depressive disorders because sedative properties of hops may accentuate depressive symptoms. Hops are commonly given as 1–2 g of dried strobile for hypnotic purposes, 0.5–2.0 mL of the liquid extract, and 1–2 mL of the tincture.\textsuperscript{5,29} Hops are often used in combination with other herbal therapies. Hops have been reported to improve sleep disturbances when used in combination with valerian.\textsuperscript{4,5,16,29}

**Melatonin**

Melatonin is a popular herbal used for its sedative properties. Melatonin is a hormone produced primarily by the pineal gland. It is used commercially by consumers to aid in the regulation of sleep. Its principal function appears to be the inhibition of reproductive activities by inhibiting gonadotropin hormones. Melatonin has been evaluated as an option to taper older patients off benzodiazepines; however, more studies are needed to establish specific protocols.\textsuperscript{35} It is commercially available as a synthetic product or derived from ani-
mal pineal tissue. It is recommended to use the synthetic version because of an increased risk of contamination or viral transmission associated with the nonsynthetic product.4,5,19,27,35

Melatonin has also been noted to reduce the efficacy of nifedipine resulting in increased blood pressure and heart rate.5,35 Melatonin is a metabolite of serotonin, so patients receiving monoamine oxidase inhibitors (including selegiline) should be warned against using melatonin and excessive amounts of tyramine-containing foods. It is also recommended to caution its use in immunocompromised patients, patients with autoimmune disorders, children, and pregnant or lactating women.5,35 Transient depression or aggravation of depressive symptoms has been reported with this product, so use in psychiatric patients is not recommended.5 Depressed patients may experience therapeutic failure from conventional or herbal therapy. Despite its popularity, the use of melatonin is not recommended in patients with depression.

Ginseng

Ginseng has been used for more than 2000 years for its purported efficacy in depression, stress management, energy enhancement, infection resistance, and aphrodisiac properties. Adverse effects that may complicate its efficacy in depressed patients include insomnia, nervousness, and poor concentration. The nervous excitation is transient, but other side effects associated with ginseng after long-term use include hypoglycemia, anticoagulation, mammary nodularity, vaginal bleeding, and gynecomastia. There is also controversy surrounding the potential for “ginseng-abuse syndrome.” The syndrome is characterized by CNS stimulation, insomnia, hypertension, diarrhea, skin eruptions, and increased motor and cognitive efficiency.5,16 Ginseng appears to enhance adrenal gland function, thus lending itself to stress management, but it negatively affects the hypothalamic-pituitary axis resulting in elevated plasma corticotropin and corticosteroid levels. Ginseng may potentiate the effects of monoamine oxidase inhibitors, stimulants (including caffeine), and haloperidol.4 There are no clinical studies proving efficacy on ginseng alone or in combination with other therapies. Long-term use of ginseng may have greater risks than benefits, and consumers should be cautious about differences within each species.

Ginkgo

Ginkgo has been used to treat cerebrovascular insufficiency, impotence, and antidepressant-induced sexual dysfunction and as an augmenting agent with conventional antidepressants. An in vitro study suggests that the dried and fresh ginkgo leaves contain flavonoids (ginkgo-flavone glycosides and bioflavonoids) that inhibit monoamine oxidase A and B, indirectly stimulate norepinephrine release by upregulating alpha-2 adrenergic receptors, and may stimulate choline uptake in the hippocampus. Side effects associated with ginkgo include headache, gastrointestinal upset and potentiation of anticoagulants.4,36

The risk of bleeding may eliminate the benefits of ginkgo as an adjunctive therapy for treating depression or any other ailment.

CONCLUSION

Despite the wide availability of herbal and dietary supplements, consumers should be cautious about using these products for the treatment of depressive disorders. Clinicians should warn patients about the potential risks associated with purity, potency, self-prescribing, and the variances associated with product formulation. Drug interactions and side effects of these products should also not be ignored. Little is known about the utilization of homeopathy, Ayurvedic, and other Chinese herbal preparations. More scientifically controlled studies are needed to assess clinical efficacy of these products compared to conventional products as well as the efficacy of certain herbal combinations.
REFERENCES

Desperately Seeking Serendipity: The Past, Present, and Future of Antidepressant Therapy


Looking back into the “dark ages” of medicine, we can see a fast evolving armamentarium of medications to treat various illnesses, including those afflicting the brain. Up until the past hundred years or so, there has been little in the way of appropriate psychiatric medication therapy. With the discovery of stimulants and opiates, a new door opened into the science of psychopharmaceuticals. Fifty years ago, the greatest leap in psychiatric medicine occurred serendipitously in the form of antipsychotics and antidepressants, some of which we still use today. The learning curve from then has been on a logarithmic scale, and we are quickly approaching the pinnacle of the curve. However, human nature has yet to catch up to scientific progress, as the stigma of mental illness is often reflected in cultural biases and nonparity with insurance benefits for medical care. Because of today’s diminishing medical and psychiatric health care benefits, we strive for superior and quicker acting drugs for these costly illnesses. The best discoveries lay ahead in the 21st century as the potential of Substance P antagonists, anti-glucocorticoids, and N-methyl-D-aspartate receptor antagonists (to name a few) are explored for their benefit in depression. Until then, we strive to understand the inner workings of the human mind to heal those with psychiatric illnesses.

KEY WORDS: history, Substance P, antiglucocorticoids, antidepressants, depression.

INTRODUCTION

Each year, depressive illnesses are estimated to cost more than $44 billion in direct and indirect costs in the United States. Comorbid illnesses such as anxiety and substance abuse only compound the complexity of depression treatment and may increase associated costs over 10-fold. Even as medical knowledge expands exponentially in areas such as genetics and immunology, our knowledge about mental illnesses is at a crawl. The most significant advances in psychiatry have only occurred by fortune and accident. Discouragingly, this may be the only way in which our next leap may arrive, for we are years, perhaps decades, away from a conceptually unified theory of the etiology and treatment of the various mental illnesses. These limitations have also been exacerbated by the systems of health care today, in which psychiatry takes second-class citizenship to more recognized “medical” illnesses. This may be due in part to an established lack of parity in insur-
ance recognition and reimbursement between mental and medical illnesses in America. Until such financial conundrums are addressed and solved, mental health care will suffer.

Depression has been recognized and described for more than 3000 years. Hippocrates, the father of modern medicine, called it “melancholia,” literally meaning “black bile,” from which he believed the depression originated. Later theories of depression were primarily religious in origin. In the eighth century BC, evil spirits were responsible. During the Middle Ages, it was felt that depression was a punishment from God for a transgression committed. Interestingly enough, these philosophies still exist in many societies around the world. It is common in some cultures to shun the mentally ill and refuse to accept a mental illness in the same context as a physical one. Sadly, these ideas are carried forth in our society through insurance reimbursement and funding issues for the mentally ill.

THE HISTORY OF PSYCHIATRIC PHARMACOLOGY

The reality of what we today term “psychopharmacology” actually began little more than 200 years ago during the age of psychiatric institutionalization. Bromide agents were “prescribed” by physicians in the 1840s as a means of decreasing anxiety and producing sedation. The practice eventually fell out of favor because of the long-term toxic effects of bromides on the central nervous system (CNS). Years later, other sedative agents were developed, some of which are still used today. These include barbiturates, paraldehyde, urethane, sulfonal, and chloral hydrate. In the latter part of the 19th century in Germany, Emile Kraepelin began a laboratory for the purposes of testing psychotropic agents in humans.

After countless millennia of having no truly effective treatments for depressive illnesses in Western medicine, stimulants were discovered. Drugs such as cocaine and caffeine were revealed to North Americans and Europeans in the 19th century by the natives of South America, who had used these drugs from their native plant derivatives for centuries. Soon thereafter, cocaine was widely available and used as a stimulant, euphoriant, nasal decongestant, and anesthetic. For consumption, an alcoholic extract named “wine of coca” was marketed, circa 1870, containing 6 mg cocaine per ounce of wine, and not long after, Coca-Cola was introduced by John Pemberton, a pharmacist in Atlanta, Georgia, in 1886 and was made with cocaine-laced syrup and kola nut. However, due to public pressure, the cocaine content was dropped from Coca-Cola in 1903.

Soon after its introduction in America, the naturally derived drug cocaine was being “studied” and prescribed by such great psychiatric physicians as Dr. Sigmund Freud, circa 1875, for its stimulant and euphoria-producing effects. In that era, cocaine use had not yet been associated with any physical or socially detrimental effects, and its use became widely accepted among the general public and professionals alike. However, in the next few decades, cocaine abuse (as well as opiate abuse) was gaining national attention, which later prompted President William Taft to address this issue before Congress in 1910. Consequently, a sharp decline in drug abuse was noted nationwide, and in 1914, abusable drugs inclusive of cocaine and opiates were banned in the United States by the Harrison Narcotics Act. Interestingly enough, Chinese physicians had been using stimulants to treat many depressive disorders for more than 5000 years in the form of the natural drug ephedrine derived from its herbal source, Ma-huang.

The discovery of the first synthesized amphetamine molecule preceded heroin’s discovery by about a decade, in 1887. At that time, chemists, such as Edeleau, were attempting to manufacture synthetic aliphatic amines. When amphetamine sulfate (Benzedrine), a congener of ephedrine, was studied, it was found to have bronchodilating, as well as sympathomimetic, properties. Several decades later, in the 1930s, reports were surfacing about its actions in the central nervous system.
It was found to “produce feelings of euphoria and relief from fatigue.”12,16 It was also noted to “improve performance on some simple tasks, increase activity levels, and produce anorexia.” Case reports from Myerson in 1936 revealed its usefulness in depression, manic-depression, and “dementia praecox.”19 These effects were useful in the initial treatment of depressive symptoms but not entirely effective on the chronic treatment of mental illness. The mood-lifting effects of the stimulants were temporary. The antidepressant effects did not persevere because of excessive release of neurotransmitters in the CNS. Once a majority of these neurotransmitters are released from their presynaptic vesicles and utilized in neurotransmission, they cannot be remanufactured quickly enough to sustain the antidepressant effect. The net effect is too much demand and not enough supply, and hence the depression returns. It would not be for several decades that another, more long-term antidepressant would be discovered.

In October 1929, shortly before the historic stock market crash, Charles Leiper Grigg of the Howdy Corporation invented 7UP, or Bib-Label “Lithiated Lemon-Lime Soda.” It promised “an abundance of energy, enthusiasm, a clear complexion and shining eyes” and is believed to be the first mass consumable antidepressant in a soft drink that was nonaddicting. The name was not well received and was changed to 7UP Lithiated Lemon Soda and then to just 7UP in 1936. The “UP” in 7UP denoted its ability to raise depressed spirits. Lithium remained as part of the recipe until the 1940s when it was removed from the American market because of toxicity.14,20,21

In Italy in 1938, Cerletti and Bini first experimented with electroconvulsive shock therapy to treat schizophrenia, mood disorders, and other psychiatric conditions.22 It quickly became the standard treatment for mental illness as there were very few viable options.11 It was deemed successful in up to 90% of cases of depression.23 Intriguingly, a device of similar parameters was discovered in America’s first psychiatric hospital in Williamsburg, Virginia, in 1793.10 It used static electricity as a source for the shock, although its usage is speculated to have been more punitive than therapeutic. In 1933, insulin shock therapy, used to induce a grand mal seizure, was also a standard treatment.11,23 For those with severe “melancholia,” a surgical technique called the prefrontal lobotomy was used to sever tracts in the frontal lobes from the rest of the brain.24 This psychosurgery was performed in thousands from 1935 until the discovery of antidepressants in the 1950s.

In the early 1900s, antidepressant compounds were not a focus of research. Instead, other medical fields such as surgery, cardiology, and medicinal chemistry took priority. Chemists concentrated their efforts on discovering antihistamines and sedatives for surgical anesthetics, as well as nonnarcotic drugs for analgesia and Parkinson’s disease.11 Forty derivatives of the compound iminodibenzyl were discovered by Häflinger and Schindler in the late 1940s and were being tested for antihistaminic effects.6 Some of these agents were fortuitously discovered to be effective antipsychotic agents.5,11 Less antihistaminic agents of this class were shelved until a Professor Roland Kuhn of Switzerland reexamined some of these chemical compounds in depressed patients and found that compound G22355, a promazine analogue, was effective.6,25 This agent was then tested in 100 depressed patients in Zurich in 1957 and later marketed as imipramine. It was the first tricyclic antidepressant; however, it really was not the very first antidepressant medication.

In the late 1940s and early 1950s, tuberculosis become a widespread epidemic and patients were isolated from society in long-term hospitals called “sanitariums” for treatment. As a matter of circumstance and pathology of the disease state, some patients became depressed. In 1951 and 1952, 2 drugs were being used to treat the tuberculosis infection: isoniazid and iproniazid.6 It was soon discovered that iproniazid, but not isoniazid, elevated the mood of the depressed patients. The anti-infective agent was then analyzed by Zeller and colleagues and discovered to inhibit the enzyme
monoamine oxidase. Additional studies afterward in the United States by Kline, Lehmann, and Crane found it to be a very effective antidepressant, for which indication it was marketed in 1958. However, due to hepatotoxicity, it was withdrawn in the United States (but not in the United Kingdom) and replaced with the less toxic monoamine oxidase inhibitor (MAOI) medication isocarboxazid.

**CURRENT RESEARCH IN DEPRESSION THERAPIES**

Analysis into the mechanisms of action of the 2 new classes of antidepressants led to new revolutionary theories about the biological basis of depression. It was several years later that scientists reported on the major chemicals of importance: noradrenaline (in 1965) and serotonin (in 1969). Soon after, alternative classes of medications were sought to address deficits in either or both of these 2 neurochemicals. The very first selective serotonin reuptake inhibitor drug discovered was fluoxetine in 1974. It took almost 14 years of research to reach the American market. From the 1970s through the 1990s, other antidepressants were serendipitously discovered or invented. They include many we use in practice today, such as trazodone (1975), citalopram (1977), sertraline (1983), paroxetine (1990), and venlafaxine (1981), which was originally developed to be used as an analgesic. As newer antidepressants are approved for therapy, the trend is toward prescribing agents with a lower risk of adverse effects. Older therapies are still in existence, yet their usage has declined significantly. As of the beginning of 2001, there are approximately 2 dozen available antidepressants on the American market (Table 1), but we have yet to truly understand the exact mechanism by which these drugs have antidepressant effects, leading to more research into alternative therapies and novel theories to describe their mechanism of action. Currently, there are approximately 26 antidepressants in the clinical testing stage for the treatment of depression, a majority of which are still based on the neurotransmitter theories of depression from decades ago.

A classic theory of the mechanism of desired antidepressant drug effects is based on the neurochemically induced down regulation of β-adrenoceptors by tricyclic antidepressant, MAOIs, and electroconvulsant therapy. Even some atypically acting antidepressants, such as iprindole, resulted in similar outcomes. Not all antidepressants were found to produce β-receptor down regulation, as some produce up regulation. Notwithstanding, another outcome consistently occurred with all tested antidepressants, which is the activation of cyclic AMP within specific brain regions.

The N-methyl-D-aspartate (NMDA) receptor is a receptor for the neurotransmitter glutamate, which is the most important excitatory transmitter in the brain. It is not only a receptor

---

**Table 1. Currently Available Antidepressant Medications**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic and heterocyclic antidepressants</td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Elavil®, Endep®</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Pamelor®</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Tofranil®</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Norpramin®</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Sinequan®, Adapin®</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>Vivactil®</td>
</tr>
<tr>
<td>Trimipramine</td>
<td>Surmontil®</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>Asendin®</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Anafranil®</td>
</tr>
<tr>
<td>Maprotiline</td>
<td>Ludiomil®</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td></td>
</tr>
<tr>
<td>Phenelzine</td>
<td>Nardil®</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>Parnate®</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Prozac®</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Celexa®</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Paxil®</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Zoloft®</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Luvox®</td>
</tr>
<tr>
<td>Serotonin norepinephrine reuptake inhibitors</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Effexor®</td>
</tr>
<tr>
<td>Atypical antidepressants</td>
<td></td>
</tr>
<tr>
<td>Trazodone</td>
<td>Desyrel®</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>Serzone®</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Remeron®</td>
</tr>
<tr>
<td>Buproprion</td>
<td>Wellbutrin®</td>
</tr>
</tbody>
</table>
but also a channel (a ligand-gated ionic channel). Recently, NMDA receptor antagonists were discovered to have antidepressant effects and may be involved in the etiology of depression. Secondary effects from NMDA receptors are a down regulation of strychnine-insensitive glycine receptors, regulation of Ca$^{2+}$ influx, and nitric oxide synthesis.

Additional effects from medications have also been observed more recently, leading to new medication developments and study. Supplemental theories on the pathophysiology of depression have evolved from endogenous neuropeptides, either through “modulation of the action on monoamine transmitters with which they coexist in a neuron” or via changes in hormone systems. At the center of this first theory is Substance P, which was discovered in 1931. Substance P belongs to a group of neuropeptides called tachykinins. Substance P’s receptor is called NK1. Studies have shown that Substance P exists in the brain, spinal cord tissue, and many other areas of the body. Substance P interacts with serotonin, also called 5-hydroxytryptophan (5-HT), and often is found cohabitating with 5-HT and norepinephrine. According to this theory, the blockade of Substance P neurons via Substance P antagonists has been associated with the relief of depression. Furthermore, on examination of rat brains following antidepressant therapy, there was a decrease in the amount of Substance P. This suggests that antidepressants may antagonize the effects of Substance P. Moreover, scientists theorize that by blocking Substance P receptors (NK1 receptors), antidepressant action can be enhanced. Merck pharmaceuticals is currently developing a potent Substance P antagonist called MK869, and further trials will be ensuing in the coming years. In initial trials, it has been shown to be as equally efficacious as paroxetine, with fewer side effects. Antiemetic indications are also being sought.

Other theories address the biological basis of depression by analysis of the hypothalamic-pituitary-adrenal (HPA) axis. Based on an old clinical finding in depressed patients, hyperactivity of the HPA axis leads to excessive glucocorticoid release and subsequent hippocampal neurotoxicity and decreased neurogenesis from early or later life trauma. New drugs in development that are based on this theory are corticotropin releasing factor R1 receptor antagonists, ketoconazole, and antiglucocorticoids. In a related neurobiological finding, a multitude of depressed patients exhibited a blunted TSH response to exogenous thyrotropin releasing hormone (TRH). Clinical relief of depression has been seen immediately following an intrathecal injection of TRH into the CNS and also with hydrocortisone administered intravenously. These studies, however, did not assess patients beyond a few days, and the lasting effects were not evaluated. Contrastingly, normalization of hormonal pathways generally occurs in 2 to 4 weeks’ time as a result of traditional antidepressant therapy.

Other complex theories about the pathogenesis of depression are being explored. Under investigation are the roles of interleukins, interferons, tumor necrosis factor, nitric oxide, prostaglandins, amino acids, growth hormone, infectious and autoimmune factors, serum cholesterol, and steroids. However, clinical trials for drugs based on these theories lag far behind conceptuality. The most likely and anticipated medications in the drug development stages are molecular variations of currently available antidepressants. Outside of that possibility, neurokinin and Substance P antagonists are showing strong promise while under investigation, as well as β-3 receptor agonists. In the “dietary supplement” category, which is outside of the Food and Drug Administration’s stringent approval process, a steroid called allopregnenolone has recently received publicity. Scientists believe allopregnenolone is related to the gamma amino butyric acid pathway and therefore when activated boosts mood-enhancing neurotransmitters. The future outlook of this theory is to find medications that will directly mimic the effects of allopregnenolone.
Considerable interest remains in natural or mechanical mood enhancers as antidepressant treatments. Behavioral and nonpharmacologic alterations, such as sleep deprivation and exposure to bright light, may offer antidepressant effects, albeit mostly temporary. Herbs that contain ephedrine and caffeine may also enhance mood and have antidepressant effects. A prospective study that followed 86,626 female nurses from 1980 to 1990 examined caffeine intake and its relationship to suicide rates. Kawachi et al. found that a strong inverse relationship existed between caffeine intake and deaths from suicide (multivariate $P$ for trend $<.001$). A theory to explain this finding relates to caffeine’s ability to stimulate the frontal cortex. It is believed that nonimpulsive suicides are more common in patients with frontal cortex understimulation, so by activating the frontal cortex, suicidal ideation is avoided. Auxiliary therapies, such as rapid transcranial magnetic stimulation and vagal nerve stimulation, may prove fruitful in the future. In April 2001, an implantable device that stimulates the vagus was approved in Canada to treat “chronic or recurrent depression in patients that are in a treatment resistant or treatment intolerant major depressive episode.”

Regardless of the exact differences in the mechanisms of each effective antidepressant, only the tolerability based on side effects and safety is of any true significance. It may not be important how each acts other than the simple fact that they initiate a biochemical cascade mechanism through 1 or more “access points” within extremely complex interactions of the brain. Perhaps each in its own way “kick starts” and sustains a process that allows the brain’s natural mechanisms to react. Theoretically, it is very much like the philosophy of homeopathic medicine with the addition of a continuation phase of treatment. One prime example of this is the European drug tianeptine, which is a selective serotonin reuptake enhancer, yielding the same net result of traditional antidepressants with a diametrically opposed mechanism.

MODELS OF CARE—CURRENT STATE OF MENTAL HEALTH CARE IN THE NATION

Even today at the beginning of the 21st century, we struggle with providing equal and adequate health care to all members of our society. The best antidepressants are only as good as the system that delivers them, and the current system of care is woefully lacking. If individuals were to provide their own insurance for treatment of psychiatric illnesses, they would be more than likely limited in the extent of their treatment by their own policy. These benefits have been likened to “starvation rations.” A great many of the large health care insurance companies encumber proper mental health care by reimbursing only a fraction of that for a mental illness versus a physical illness. Outpatient treatment can be curtailed to a modicum of visits to a therapist or day treatment facility. A federal survey of 1656 employers across the nation revealed that 14% were out of compliance with the Federal Mental Health Parity Act, which requires “employer-sponsored health plans to have annual and lifetime dollar limits for mental health coverage that are no more restrictive than those for all medical and surgical coverage.” However, it does not state that lifetime limits or treatment days cannot be limited. As many as 87% of compliant employers were found to have imposed such restrictions. In addition, copayments for these services may be prohibitive for the patient to pay or practitioner to accept. In the past 10 to 15 years, psychiatric inpatient beds in public hospitals have declined from 130,000 beds to less than 80,000. In addition, those with more severe illnesses are encompassing a majority of hospital beds, as those with less severe illnesses use outpatient services. More recently, psychiatrist numbers have declined as evidenced by fewer psychiatric residents and positions available. Diminishing reimbursement has also affected physician salaries, and in 1996, psychiatrists were ranked as the lowest paid physicians in America. Most of the psychiatric care today is pro-

JOURNAL OF PHARMACY PRACTICE, Volume 14, Number 6, December 2001
vided by primary care practitioners, who receive limited training in psychiatry and psychopharmaceuticals. All in all, this leads to a diminished milieu of care. To keep up with quickly vanishing resources, the treatments today must be more effective, quicker acting, or better tolerated.

Psychiatric services may account for 10% of direct health care expenditures nationwide, yet most insurance companies allocate only 3%–5% to mental health. In 1998, a study of health plans of medium and large American employers found a trend from 1988 to 1997 of an overall decrease in behavioral health care benefits in relation to total health benefits. The amount decreased from 6.1% to 3.1% in the 9-year span. Because mental illness, particularly depression, incurs indirect costs on society (i.e., lost wages and work productivity), such a low allocation could have an exponential rippling effect on the economy. On average, the costs incurred with depression may be greater than with most other medical illnesses. Factoring into the equation the economic strife of the depressed person, a downward spiral ensues. Many of the depressed may end up depending on social assistance. A Canadian survey found that 45.4% of single parents on social assistance had a depressive illness. Furthermore, reimbursement over the past 10 years for face-to-face services has been cut in half and still continues to decline, yet no medications have been developed that act quickly.

In addition to the stigma of mental illness, those who have the courage to seek out help are often given inadequate care. It is estimated that only one third of adults with depression or anxiety receive adequate treatments for their disorder. A telephone survey by Young et al. of California discovered that only 20% of those who seek out professional care receive appropriate medications. Only 31% received any counseling, with 17% receiving “appropriate” counseling. Correlating factors to appropriate care include female sex, Caucasian race, and adults between ages 20 and 59. Added factors for inadequate depression treatment include a withholding of the diagnosis of depression by physicians. A study by Dr. Crystal et al. examined medical records of Medicare patients from 1992 to 1996. They found that Medicare patients were 1.5 times less likely to have a diagnosis of depression if they lacked supplemental insurance coverage. Furthermore, elderly patients (those more than 75 years of age) were less likely to receive any treatment for depression and even more unlikely to receive pharmacotherapy versus psychotherapy for treatment.

Compounding these low conversion rates are managed care’s resistance to certify for inpatient hospitalizations. A recent study of 100 subsequent patients who presented to the emergency room at a Florida hospital after attempting suicide endeavored to ascertain if managed care’s criteria for admission for suicidal patients are rational. The criteria included that a patient must have a specific plan to be admitted to the inpatient hospital unit. The study found that 84% of the patients who made a suicide attempt did so with no specific plan or had acted impulsively. Therefore, only 16% of these patients would be certified for admission under the managed care criteria. Such studies prompted a publication in 1999 to prevent suicide by the U.S. Public Health Service and Surgeon General.

Another trend has been seen in psychiatric hospitals in addition to shorter patient lengths of stay. This is the weakening of program structure in the evening hours and on the weekends. For example, a patient admitted to the hospital on a Friday evening and discharged on Monday morning would not receive the same group therapy or services as someone whose length of stay was mostly during weekdays. The difficulty in providing consistency of therapy and services equally is in the continually declining reimbursement for psychiatric services and an inability to hire extra staff at shift-differential pay scales. As skilled labor costs suffer, so do the demands for such positions. Many staff in psychiatry are not expecting to become
wealthy in their careers. The most passion and zeal from staff usually stem from an altruistic desire to limit or end human suffering.

As it is difficult to measure mental wellness, the demand for more documentation of patient progress and behaviors rises. Those who actually do most charting are the nurses who spend much of their day behind a desk or computer instead of in direct patient contact. The quality of therapies also suffers as reimbursement for psychological services declines or is difficult to obtain.\textsuperscript{55,60} Much of the inpatient and outpatient psychotherapy is performed by psychiatric assistants, recreation therapists, and social workers, not by psychiatrists or psychologists, as their time is too costly to provide these services.\textsuperscript{58}

\section*{CONCLUSION}

\textit{The Future}

Many believe that in the next 25 years a cure for mental illness will be developed, through drug therapy or, more likely, through bioneuro-modulators specifically designed and tailored to each individual’s neurochemistry. Even the idea of genetic screening and repair may be possible before someone predisposed to a mental illness experiences his or her first symptom. Prospective studies are greatly needed to help determine those at physiologic risk for depression, as has been done in the United Kingdom.\textsuperscript{70} Until such time, much social reform and education must take place to destigmatize mental illness and provide parity in insurance coverage. Recognition of psychiatric disorders as neurologically and chemically based illnesses must be accompanied by strengthened financial and political support.\textsuperscript{55,56} Only then can the philosophies trickle down through the masses to construct a viable medium for large-scale change.

Another serotonergic or noradrenergic medication unfortunately will not help psychiatric medicine to evolve. Notwithstanding, medication therapy today is greatly advanced over that available a hundred years ago, but we are no closer today to a comprehensive understanding of mental illness than we were at that time in history.\textsuperscript{42}

Only research on the underlying etiology of mental illnesses can do this. The key to designing effective future treatments must be through the absolute recognition of how a disease state affects the brain tissue, from a submolecular level to the quantum level. Our current theories were only developed based on our knowledge of past drugs’ action on the brain of animals.\textsuperscript{42} This is reverse logic, similar to a person looking at the \textit{Mona Lisa} and trying to speculate what da Vinci consumed for supper the night before he painted it. Educated guesses aside, it ideally should be rationalized in reverse. We need to design drugs based on correcting known biological or biochemical malfunctions. However, our current hypotheses are based on secondhand conjecture and speculation, and this is the best today’s science can offer. Overall, the need for prospective research in this area is clear. In the years to come, we can hope that our technology will allow us to see inside the inner workings of our brains and may let us truly understand its proper function. Only then will we begin to design an ideal and truly effective treatment and perhaps someday a cure.

\section*{REFERENCES}


**AUTHOR INDEX**

<table>
<thead>
<tr>
<th>Author Name</th>
<th>Page Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abu-Shanab, J.R.</td>
<td>526</td>
</tr>
<tr>
<td>Alfaro, C.</td>
<td>467</td>
</tr>
<tr>
<td>Altmann, A.</td>
<td>383</td>
</tr>
<tr>
<td>Anderson, P.D.</td>
<td>2, 162, 356, 443</td>
</tr>
<tr>
<td>Anderson, S.L.</td>
<td>540</td>
</tr>
<tr>
<td>Avent, M.</td>
<td>181</td>
</tr>
<tr>
<td>Beauchesne, M.-F</td>
<td>126</td>
</tr>
<tr>
<td>Bednarczyk, E.M.</td>
<td>298, 308</td>
</tr>
<tr>
<td>Bell, E.A.</td>
<td>88</td>
</tr>
<tr>
<td>Bertridge, M.S.</td>
<td>416</td>
</tr>
<tr>
<td>Blake, K.</td>
<td>89, 164, 228</td>
</tr>
<tr>
<td>Blasberg, R.G.</td>
<td>376</td>
</tr>
<tr>
<td>Botts, S.R.</td>
<td>467</td>
</tr>
<tr>
<td>Bourdet, S.V.</td>
<td>108</td>
</tr>
<tr>
<td>Branch, E., III</td>
<td>560</td>
</tr>
<tr>
<td>Brock, T.P.</td>
<td>277</td>
</tr>
<tr>
<td>Brown, T.F.</td>
<td>407</td>
</tr>
<tr>
<td>Buscini, S.M.</td>
<td>443</td>
</tr>
<tr>
<td>Chagan, L.</td>
<td>54</td>
</tr>
<tr>
<td>Cohen, H.</td>
<td>4</td>
</tr>
<tr>
<td>Cohen, V.</td>
<td>162</td>
</tr>
<tr>
<td>Coile, D.</td>
<td>181</td>
</tr>
<tr>
<td>Cooke, S.C.</td>
<td>498</td>
</tr>
<tr>
<td>Cooper, D.J.</td>
<td>407</td>
</tr>
<tr>
<td>Cooper, M.D.</td>
<td>407</td>
</tr>
<tr>
<td>Corelli, R.L.</td>
<td>143</td>
</tr>
<tr>
<td>DiGregorio, R.V.</td>
<td>41</td>
</tr>
<tr>
<td>Dominguez, K.D.</td>
<td>166</td>
</tr>
<tr>
<td>Dopheide, J.A.</td>
<td>488</td>
</tr>
<tr>
<td>Doudet, D.J.</td>
<td>341</td>
</tr>
<tr>
<td>Dugan, D.J.</td>
<td>458</td>
</tr>
<tr>
<td>Dupuis, R.E.</td>
<td>258</td>
</tr>
<tr>
<td>Emanuel, A.M.</td>
<td>511, 551</td>
</tr>
<tr>
<td>Fann, A.L.</td>
<td>258</td>
</tr>
<tr>
<td>Finch, D.A.</td>
<td>6</td>
</tr>
<tr>
<td>Fung, H.B.</td>
<td>6</td>
</tr>
<tr>
<td>Ghazvini, P.</td>
<td>551</td>
</tr>
<tr>
<td>Goins, B.A.</td>
<td>397</td>
</tr>
<tr>
<td>Goren, J.L.</td>
<td>478</td>
</tr>
<tr>
<td>Haberkorn, U.</td>
<td>383</td>
</tr>
<tr>
<td>Hoang, D.Q.</td>
<td>70</td>
</tr>
<tr>
<td>House, N.A.</td>
<td>453</td>
</tr>
<tr>
<td>Hudmon, K.S.</td>
<td>143</td>
</tr>
<tr>
<td>Iglesias, A.J.</td>
<td>560</td>
</tr>
<tr>
<td>Jaronczyk, D.P.</td>
<td>2</td>
</tr>
<tr>
<td>Kapur, S.</td>
<td>332</td>
</tr>
<tr>
<td>Kaszuba, M.</td>
<td>2</td>
</tr>
<tr>
<td>Kelly, H.W.</td>
<td>89, 91, 164</td>
</tr>
<tr>
<td>Kendrach, M.</td>
<td>256</td>
</tr>
<tr>
<td>Kinnunen, L.H.</td>
<td>407</td>
</tr>
<tr>
<td>Kleyman, E.</td>
<td>54</td>
</tr>
<tr>
<td>Kroon, L.A.</td>
<td>143</td>
</tr>
<tr>
<td>Kuczynski, S.</td>
<td>6</td>
</tr>
<tr>
<td>Kuhn, R.J.</td>
<td>207</td>
</tr>
<tr>
<td>Lammertsma, A.A.</td>
<td>361</td>
</tr>
<tr>
<td>Larose-Pierre, M.</td>
<td>560</td>
</tr>
<tr>
<td>Larsen, J.</td>
<td>228</td>
</tr>
<tr>
<td>Laven, D.L.</td>
<td>296, 308, 358</td>
</tr>
<tr>
<td>Lee, Z.</td>
<td>416</td>
</tr>
<tr>
<td>Lumberg, K.P.</td>
<td>258</td>
</tr>
<tr>
<td>Marken, P.A.</td>
<td>444</td>
</tr>
<tr>
<td>Mathai, L.</td>
<td>181</td>
</tr>
<tr>
<td>Melanson, R.</td>
<td>356</td>
</tr>
<tr>
<td>Metz, J.M.</td>
<td>407</td>
</tr>
<tr>
<td>Moore, T.R.</td>
<td>511, 551</td>
</tr>
<tr>
<td>Nelson, L.A.</td>
<td>526</td>
</tr>
<tr>
<td>Norwood, D.A.</td>
<td>560</td>
</tr>
<tr>
<td>Overman, G.P.</td>
<td>540</td>
</tr>
<tr>
<td>Patton, M.</td>
<td>256</td>
</tr>
<tr>
<td>Phillips, W.T.</td>
<td>397</td>
</tr>
<tr>
<td>Prokhorov, A.V.</td>
<td>143</td>
</tr>
<tr>
<td>Ramos, L.</td>
<td>6</td>
</tr>
<tr>
<td>Rappa, L.R.</td>
<td>560</td>
</tr>
<tr>
<td>Robinson, C.A.</td>
<td>207</td>
</tr>
<tr>
<td>Rozenfeld, V.</td>
<td>54</td>
</tr>
<tr>
<td>Rudis, M.I.</td>
<td>70</td>
</tr>
<tr>
<td>Sadelain, M.</td>
<td>376</td>
</tr>
<tr>
<td>Sanoski, C.A.</td>
<td>18</td>
</tr>
<tr>
<td>Schmidt, M.E.</td>
<td>427</td>
</tr>
<tr>
<td>Shreve, M.S.</td>
<td>143</td>
</tr>
<tr>
<td>Simon, W.A.</td>
<td>560</td>
</tr>
<tr>
<td>Sommi, R.W., Jr.</td>
<td>453</td>
</tr>
<tr>
<td>Stoner, S.C.</td>
<td>448</td>
</tr>
<tr>
<td>Taber, D.J.</td>
<td>258</td>
</tr>
<tr>
<td>Tracey, I.</td>
<td>368</td>
</tr>
<tr>
<td>Tucker, M.L.</td>
<td>498</td>
</tr>
<tr>
<td>Verhoeff, N.P.L.G.</td>
<td>332</td>
</tr>
<tr>
<td>Wehner, J.S.</td>
<td>448</td>
</tr>
<tr>
<td>Williams, D.</td>
<td>89, 108, 164</td>
</tr>
<tr>
<td>Williams, D.M.</td>
<td>277</td>
</tr>
<tr>
<td>Wise, R.G.</td>
<td>368</td>
</tr>
</tbody>
</table>

**SUBJECT INDEX**

<table>
<thead>
<tr>
<th>Subject Name</th>
<th>Page Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcysteine</td>
<td>207</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>70</td>
</tr>
<tr>
<td>Acute severe asthma</td>
<td>91</td>
</tr>
<tr>
<td>Adolescents, depression management</td>
<td>488</td>
</tr>
<tr>
<td>Advanced cardiac life support</td>
<td>41</td>
</tr>
<tr>
<td>Aerosol</td>
<td>277</td>
</tr>
<tr>
<td>Aerosolized antibiotics</td>
<td>207</td>
</tr>
<tr>
<td>Allergic rhinitis, management of</td>
<td>228</td>
</tr>
<tr>
<td>Alternative therapies, depression considerations</td>
<td>551</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>308</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>41</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>207, 228</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>488, 540</td>
</tr>
<tr>
<td>Antidepressant agents</td>
<td>453</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>526, 560</td>
</tr>
<tr>
<td>Antiglucocorticoids</td>
<td>560</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>228</td>
</tr>
<tr>
<td>Antimicrobial agents</td>
<td>70</td>
</tr>
<tr>
<td>Antimicrobial mechanisms</td>
<td>6</td>
</tr>
<tr>
<td>Antipsychotics, neuroimaging role in treatment development</td>
<td>332</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>18</td>
</tr>
</tbody>
</table>
INDEX

Assessment, 448
Asthma
  acute management, 91
  chronic management considerations, 108
Augmentation, 478
β2-agonists, 91
Book reviews
drug injury, 162
drug interaction in infectious diseases, 2
infectious diseases antimicrobial management, 356
mother’s milk and dedication, 3
pediatric dosage handbook, 88
pharmacist disease management credentialing, 256
Bronchiolitis, RSV treatment and prevention, 166
Bronchodilators, 108, 126, 207
Bronchopulmonary dysplasia, 181
Cancer, 383
Cancer therapy, PET in tumor response evaluating, 361
Cardiac resuscitation, pharmaco-therapeutic advances in, 41
Cardiology, 18
Cardiovascular disease, depression treatment management, 526
Cardiovascular diseases, 70
Central nervous system, functional neuro-PET imaging assessing, 308
Cerebral blood flow, 407
Cerebral glucose metabolism, 407
Cerebrovascular disease, 308
Children, depression management, 488
Chronic lung disease, 181
Cognitive, 488
COPD, 126
Corticosteroids, 91, 108, 126, 207
Critical care medicine, 70
Cyclooxygenase-2 inhibitors, 54
Cystic fibrosis, pulmonary disease management, 207
Cytochrome P-450 system, 467
Decongestants, 228
Dementia, 308
Depression, 308, 478, 488, 498, 511, 526, 540, 551, 560
evaluating techniques and tools, 448
therapeutic goals attaining, 453
Disease progression, 341
Dopamine system, 341
Dornase alfa, 207
Drug development
  imaging role in, 296, 358
  new drug availability acceleration, 407
  pharmacological MRI, 368
  scintigraphic imaging during liposome, 397
Drug interactions, antidepressant, 467
Drug selection, 458
Drug therapy outcomes, imaging role in, 358
Dry powder inhaler, 277
Dyslipidemia, 18
Elderly, 498
Epilepsy, 308
Erythropoiesis, 70
Evaluation, 448
Extended-spectrum beta-lactamases, 6
FDG, 298
5-iodo-2’-fluoro-1-β-d-arabinofuranosyl-uracil, 376
Fluorodeoxyglucose, 361
Functional imaging, 427
Functional magnetic resonance imaging (fMRI), 332, 368, 407
Gastroenterology, 70
Gene therapy, 207
  imaging techniques for, 383
  imaging transgene expression, 376
Geriatric, depression, 498
Gram-negative resistance, beta-lactamases extended-spectrum and inducible, 6
Heart failure, 18
Hematology, 70
Herbs, 551
Herpes simplex virus, 376
HIV/AIDS, depression treatment dilemma, 376
Hormones, 511
Hypertension, 18
Ibuprofen, 207
Inducible beta-lactamases, 6
Infectious diseases, 70
Infliximab, 54
Inhalation delivery devices, clinical considerations in, 277
Inhaled antibiotics, 207
Intensive care medicine, 70
Intranasal corticosteroids, 228
Ipratropium bromide, 91
Ischemic heart disease, 18
Leflunomide, 54
Leukotriene inhibitors, 108
Life span, 511
Ligands, 427
Liposomes, 397
Lung disease, neonatal chronic, 181
Lung transplantation, 258
Macrolides, 207
Magnesium sulfate, 91
Magnetic resonance imaging (MRI), 368, 383
Metabolic imaging, 427
Metered-dose inhaler, 277
Mood, 551
Nebulizer, 277
Neonatal, 181
Nephrology, 70
Neuroimaging, 368
Neurology, 70
Neuromuscular blockage, 70
Neuropharmacology, 308
Obsessive-compulsive disorder, 308
Pancreatic enzymes, 207
Parkinson’s disease, 308
  radionuclide imaging in, 341
Pharmacist, 143
Pharmacodynamic geriatric depression, 498
Pharmacokinetics, 207, 498
Pharmacology, 368
Pharmacotherapy, 70
  functional imaging clinical outcomes monitoring, 298
Pharmacy practice
depression—treatable public health problem, 444
pharmacotherapy frontiers, 4
pulmonary medicine, 88, 164
radiologic pharmacy, 358
pHMR, 368
Positron emission tomography (PET), 298, 308, 332, 341, 361, 376, 383, 397, 407, 427
Pregnancy, 511
Pulmonary disease
  chronic obstructive management, 126
  smoking cessation pharmacist role, 143
Radiologic pharmacy, imaging role in drug development, 358
Radionuclide imaging, 397
Rating scales, 448
Receptor affinity, 458
Recurrence, 453
Refractory depression, treatment strategies, 478
Remission, 453
Respiratory syncytial virus, 166
Response, 453
Rheumatoid arthritis, 54
Rheumatology, 54

St. John’s wort, 551
Sam-E, 551
Schizophrenia, 308, 332
Scintigraphy, 397
Sedation, 70
Sepsis, 70

Seredipity, antidepressant therapy and, 560
Single photon emission computed tomography (SPECT), 298, 332, 341, 383s
Sinusitis, management of, 228
Smoking cessation, 143
SSRI, 467, 498
Substance abuse, 540
Substance P, 560
Suicide, 498
Suicide genes, 383
Switching, 478

TCA, 467
Technetium-99m, 397
Thymidine kinase, 376
Tomography emission computed, 298
Tumor response, 361

U.S. pharmacopeial convention, 443
Vasopressin, 41

Women, depression across life cycle, 511